

Early Stratification of Sepsis Using Presepsin in Emergency Department (North-East of Romania Experience)

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Sepsis syndrome is a common and have devastating implications on health care systems worldwide. Biomarkers may have an important role to highlight the presence, absence or severity of sepsis. Retrospective study was conducted on a group of 81 patients with suspected sepsis, presented in the Emergency Department - Emergency County Hospital St. Spiridon Iasi during 01.09.2014-30.10.2014. The obtained statistical data's were interpreted using SPSS software and the ROC curve was calculated. The study aims was to establish the following: determining the validity of presepsin as a biological marker in sepsis diagnosis and prognosis; sepsis stratification. The mean age of patients was 64.52 years. Determination of presepsin sensitivity in sepsis early diagnosis was calculated by generating the ROC curve. Following AUC values were found: AUC = 0.709, with a standard error of 0.065 for predicting sepsis; AUC = 0.866, with a standard error of 0.080 for severe sepsis; AUC = 0.864, with a standard error of 0.053 in the presence of septic shock. The average values of presepsin, related with severity of infection, it was found to be 544.39 ± 141.93 pg./mL in case of localized infection; 605.6 ± 59.55 pg./mL in patients with systemic inflammatory response syndrome; 1283.21 ± 195.74 pg./mL in patients diagnosed with sepsis; 4787.8 ± 1980.43 pg./mL in patients presenting severe sepsis and 3734.88 ± 1732.41 pg./mL in patients diagnosed with septic shock. Presepsin level, measured by using quantitative dosage methods, may be helpful in staging patients diagnosed with sepsis and may be used as an indication for initiation of intensive therapy to prevent septic shock. Presepsin level can be used as an early marker of severe prognostic in septic patients.

Keywords: emergency department, sepsis, biomarker, presepsin

Sepsis is defined as an infectious disease, evolving as a serious systemic infection and will progress to severe sepsis (acute organ dysfunction caused by an infection or suspected to be caused by an infection) and to septic shock (severe sepsis associated with hypotension that does not respond to fluid resuscitation therapy), installed as a result of delivery in the blood of pathogens, toxins and cellular disintegration products. Sepsis and its clinical forms must be regarded as stages of the same disease [1].

Despite progress in antibiotic therapy, sepsis remains a common and have devastating implications on health care systems worldwide. Estimated average annual cost for care of patients with sepsis was calculated to be worth \$ 16.7 billion in the year 2008 [2].

This pathology is a challenge to overcrowded emergency services. Failure to recognize this entity at the appropriate time, followed by early initiation of therapy and supportive etiological can lead to degradation of vital parameters or even death in these patients. Hence the need for the use of laboratory diagnostic methods easy to use with high sensitivity and specificity to allow an early diagnosis, available in short time in emergency departments (ED).

Biomarkers may have an important role to highlight the presence and severity of sepsis [3-8].

Presepsin (sCD14-ST) - CD 14, is a glycoprotein expressed on the cell membrane surface of monocytes and macrophages present in macrophages, monocytes and granulocytes, is responsible for intracellular signal transmission triggered by the presence of endotoxins. Soluble fraction was called soluble CD14 subtype or presepsin has proved to present increased plasma levels in infections [6-8]

Cut-off value of presepsin, allowing systemic inflammatory response syndrome differentiation within bacterial infectious diseases and nonbacteriene it was found at 600 pg / mL with a sensitivity of 87.8% and a specificity of 81.4% [3].

Experimental part

Materials and methods

This is a prospective study, conducted on a group of 81 patients which presents clinical signs of infection, out of a total of 10483 patients presented in the Emergency Department - Emergency County Clinical Hospital St. Spiridon Iasi, during 01.08.2014-30.10.2014.

The study aims to establish the following:

- Determining the validity of presepsin as biological marker of sepsis diagnosis and prognosis; sepsis stadialization; intrahospital mortality at 28 days after presenting in Emergency Department and admition on clinical wards.

The study protocol included the following group of data: epidemiological, clinical and laboratory variables, elements of therapy administrated when patient is presenting in the Emergency Department - Hospital St. Spiridon - Iasi, evolution in 28 days.

Inclusion criteria:

- Patients over 18 years.
- Patients with clinical signs of infection accompanied by the presence of at least two of the following criteria: temperature > 38°C or < 36°C; heart rate > 90 / min; respiratory rate > 20 / min; leukocytosis (>12,000 mm³) or leukopenia (<4000 mm³).

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Exclusion criteria:

- Patients under 18 years of age
- Pregnant or lactating womans.

The diagnosis of sepsis was made based on the usually clinical signs in conjunction with other investigations, according to the diagnostic criteria of Surviving Sepsis Campaign [4].

For each patient with suspected sepsis in the ED the approach was standardized: clinically evaluation, vital signs were monitored, clinical and laboratory data were recorded in patient case sheets and they received therapeutic measure according to ED diagnosis.

Sepsis was defined as the clinical suspicion of infection together with at least two features of the systemic inflammatory response syndrome (heart rate > 90 bpm; respiratory rate > 20/min; temperature > 38.3°C or < 36°C; altered mental status; blood glucose > 140 mg/dL in a nondiabetic patient; and white cell count < 4000/ μ L or > 12 000/ μ L) [4].

Severe sepsis was defined as sepsis with evidence of organ dysfunction (systolic blood pressure < 90 mmHg or mean arterial pressure < 65 mmHg; increased FiO₂ requirement to keep SpO₂ > 90%; urine output < 0.5 mL/kg/h; creatinine > 2mg/dL; bilirubin > 2mg/dL; platelets < 100000 μ L, international normalized ratio > 1.5; lactate > 2 mmol/L) [4].

Septic shock was defined as severe sepsis plus hypotension despite adequate fluid resuscitation (4). The study was approved by the University of Medicine and Pharmacy Gr.T.Popa Iasi ethics committee. Data collected from records meeting inclusion criteria were statistically processed using statistical analysis software SPSS V.22 IBM.

Results and discussions

Structural in study group there is a slight predominance of females patients (51.85%). Average age was 64.52 years, with a standard deviation of 15.36 years.

After completion of all clinical investigations and laboratory, 33.33% from patients were diagnosed with sepsis, including patients with sepsis 17.28%, severe sepsis 6.17% and septic shock 9.88%, the rest of them having SIRS 58.02% or localised infection 8.64%.

A percentage of 22.22% were admitted on intensive care unit after evaluation, diagnostics and therapeutics procedures initiated in ED.

The biochemical parameters were determined, needed to support the diagnosis in ED, including the CBC, from which were used the values of leukocytes, platelets and hemoglobin, pH and alkaline reserve, lactate, C-reactive protein, urea and creatinine (to monitor renal function), blood glucose determination.

Table 1 describes the characteristics of the patients in terms of clinical and laboratory values, grouped by diagnosis. The table values describe the mean of clinical or laboratory parameters with corresponding standard deviation of each parameter.

The presepsin value were determined for all patients, the average value was 1284.65 pg/mL. The correlations between the presepsin value and presence of sepsis, severe sepsis and septic shock were calculated statistically. The result showed a positive correlation, statistically significant, between presepsin value and subsequent presence of sepsis, severe sepsis and septic shock, a value of 0.439 with a $p = .0001$, meaning a direct link between the two variables.

The ROC curve was drawn, to highlight the correlation between the presepsin values and sepsis in the study group,

Table 1
CLINICAL AND BIOLOGICAL VALUES

	Diagnosis									
	Infection		SIRS		Sepsis		Severe sepsis		Septic shock	
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation
GCS	15.00	.000	14.66	1.340	13.86	2.770	14.80	.447	12.00	4.660
SBP	142.43	41.896	128.85	23.323	134.86	32.503	137.60	36.774	105.13	50.848
DBP	74.71	16.163	73.28	11.943	73.00	12.172	69.00	22.517	52.63	18.213
RF	17.71	2.360	19.11	6.291	21.57	7.144	21.00	8.000	22.50	8.384
CF	113.57	34.626	89.66	21.802	99.71	22.221	82.80	16.947	105.88	25.776
SpO ₂	96.428 6%	3.99404 %	97.0213 %	3.94246 %	94.7857 %	6.82956 %	98.0000 %	3.46410 %	95.0000 %	6.63325 %
Leucocytes	14.551 4	6.50720	13.1594	6.61023	16.3014	8.77088	22.8260	14.8271 8	15.8075	6.43294
Haemoglobin	11.657	2.0403	12.155	2.2863	11.529	2.8505	10.000	1.6186	12.125	2.2796
Thrombocytes	253.71	160.292	269.15	134.898	232.21	95.133	255.00	149.491	180.00	89.790
Urea	70.00	49.675	42.32	21.650	73.71	51.241	162.80	211.998	111.75	73.036
Creatinine	1.1757	1.00955	1.1164	.54018	1.7314	1.11443	5.4800	8.01922	2.1275	.90698
Glycaemia	179.86	80.157	162.64	97.937	214.07	82.580	165.40	62.572	157.63	69.463
Lactate	1.371	.5155	2.304	3.1347	1.914	.8857	1.700	.8000	15.300	24.9644
RA	23.440	6.8606	25.015	3.9347	22.625	4.5842	17.120	7.5612	21.088	5.4635
pH	7.4171	.05559	7.3855	.36062	7.4400	.07411	7.3800	.17507	7.0688	.84218

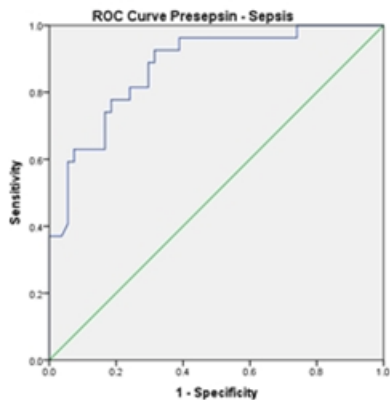


Fig. 1. ROC Curve Presepsin - Sepsis

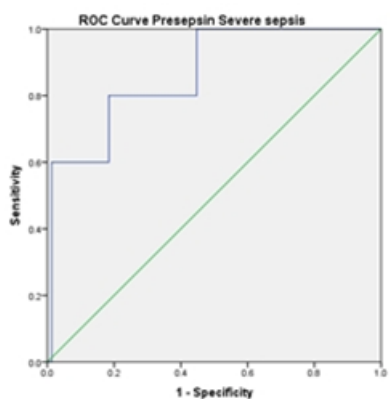


Fig. 2. ROC Curve Presepsin - Severe sepsis

the resulting area under the curve (AUC) had a value of 0.709 with a standard error of 0.065 (fig. 1). After obtaining these values we can say that the probability that a patient from our study to present sepsis is high if presepsin values is higher than 340 pg/mL, within the range of 340 pg/mL - 2724 pg/mL.

We drew also the ROC curve to highlight the relationship between the presepsin values and the presence of severe sepsis, the area under the curve in this case taking a value of 0.866 with a standard error of 0.080, the predictive power of the likelihood of sepsis where an average presepsin value is 4787.80 pg/mL is high (fig. 2).

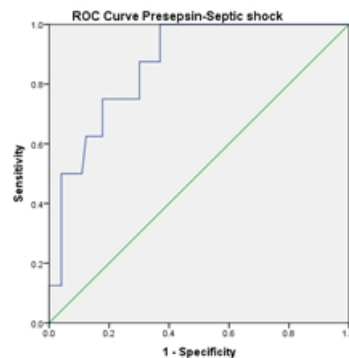


Fig. 3. ROC Curve Presepsin - Septic shock

Finally we drew ROC curve for presepsin and presence of septic shock, the resulting value of AUC being in this situation of 0.864, with a standard error of 0.053, obtaining a high predictive value between the determined value of presepsin and presence of septic shock (fig. 3).

In table 2 are described the average value of presepsin related with severity of infection. The cut-off value calculated from our statistic was 345.5 pg/mL in sepsis with sensitivity of 92.9%; 750 pg/mL with sensitivity 80% in case of severe sepsis and 817.5 pg/mL with sensitivity 87.5% in case of septic shock.

The average age of patients with sepsis, described in the literature, has increased over time, from an average of 64.1 years up to 68.2 years, the average obtained in the present study were of the 64.52 years [5].

Presepsin is described in recent literature as an independent variable that can be associated with the prediction of survival to 28 days and his prognostic accuracy is increased compared with other biomarkers, including procalcitonin [8-10,12-15].

AUC value obtained in our study were 0.709, with a standard error of 0.065 for the prediction of sepsis in the study lot; AUC=0.866 with a standard error of 0.080 in cases of severe sepsis with an average presepsin value of 4787.80 pg/mL; AUC=0.864, with a standard error of 0.053, again

Table 2

MEAN VALUE PRESEPSIN RELATED WITH SEVERITY OF INFECTION

	Stadialization		Statistic	Std. Error
Presepsin	Localized infection	Mean	544.39	141.938
		95% Confidence Interval for		
		Lower Bound	197.08	
	SIRS	Mean	891.70	
		Upper Bound		
		Mean	605.60	59.556
	Sepsis	95% Confidence Interval for		
		Lower Bound	485.72	
		Upper Bound	725.47	
	Severe sepsis	Mean	1283.21	195.748
		95% Confidence Interval for		
		Lower Bound	860.33	
	Septic shock	Mean	1706.10	
		Upper Bound		
		Mean	4787.80	1980.439
		95% Confidence Interval for		
		Lower Bound	-710.78	
		Upper Bound	10286.38	
		Mean	3734.88	1732.419
		95% Confidence Interval for		
		Lower Bound	-361.65	
		Mean	7831.40	
		Upper Bound		

obtaining a predictive value, positive, between the determined value of presepsin and presence of septic shock. AUC values we obtained are comparable with the values in the few studies published so far, they have published AUC values between 0.640 to 0.790 for predicting the value presepsinemicie sepsis [9,10].

The correlation between the presepsin level and presence of septic shock was recently described in the literature [1]. In our study we found positive correlation, statistically significant, between level of presepsin determined in our study group patients and subsequent presence of sepsis, severe sepsis and septic shock, the calculated value of 0.439 with a $p = 0.000$, meaning a direct link between this two variables.

The average values of presepsin, related with severity of infection, obtained in our study were 544.39 ± 141.93 pg./mL in case of localized infection; 605.6 ± 59.55 pg./mL in patients with systemic inflammatory response syndrome; 1283.21 ± 195.74 pg./mL in patients diagnosed with sepsis; 4787.8 ± 1980.43 pg./mL in patients presenting severe sepsis and 3734.88 ± 1732.41 pg./mL in patients diagnosed with septic shock. In literature we find only a few studies which analyze this correlation, and the result seems to be in the same area of average results. Shozushima et al describe the following average values of presepsin: 294.2 ± 121.4 pg / mL in patients without infection; 721.0 ± 611.3 pg / mL in patients with local infection; 333.5 ± 130.6 pg / mL for systemic inflammatory response syndrome; 817.9 ± 572.7 pg / mL in patients diagnosed with sepsis and 1992.9 ± 1509.2 pg / mL in patients with severe sepsis [16]. Resulting AUC value in the evaluation of presepsin level as predictive for severe prognostic was 0.764 with a standard error of .062, a value that allows the statement that in this situation presepsin can help clinician in decision to apply more aggressive therapy from the first moments.

We are aware that our study has some limitation. First limitation is that it is a single-center study, in the major university hospital from North-East of Romania, and we only included patients presenting to ED with sepsis suspicion; direct referrals from other medical specialty and patients developing sepsis in hospital were not included.

Conclusions

Presepsin, measured by using quantitative dosage method may be helpful in staging patients diagnosed with sepsis and may be used as an indication for early initiation of intensive therapy to prevent installing of septic shock on patients with elevated values.

Presepsin can be useful as an early marker of mortality in septic patients.

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Manuscript received: 18.11.2016

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