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Utility of presepsin (sCD14-ST) as a diagnostic and prognostic marker of sepsis in the emergency department

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Abstract

Background: Presepsin (PSEP) is released during infectious diseases and can be detected in the blood. PSEP has shown promising results as sepsis marker. We examined the diagnostic and prognostic validity of PSEP in patients suspicious of sepsis on admission in the emergency department (ED).

Methods: One hundred twenty three patients with signs of SIRS and/or sepsis and 123 healthy individuals were enrolled. PSEP was determined on admission, after 8, 24 and 72 h.

Results: Mean PSEP concentrations of the control group and the patient group were 130 and 1945 pg/ml. PSEP differed between SIRS, sepsis, severe sepsis and septic shock and showed strong association with 30-day mortality ranging from 10.3 % in the 1st to 32.1% in the 4th quartile. The ROC curve analyses revealed an AUC value of 0.743. Combined assessment of PSEP and MEDS score increased the AUC up to 0.878 demonstrating the close relationship with outcome. Based on the PSEP values in the different severity degrees, decision thresholds for risk stratification were established. The course of PSEP during the first 72 h was associated with effectiveness of treatment and outcome.

Conclusions: PSEP allowed outcome prediction already on admission to a similar degree as the clinical scores MEDS and APACHE II. Combination of PSEP with MEDS score improved the dicriminatory power for outcome prediction.

Keywords: Presepsin, Emergency department, Sepsis, Diagnosis
Prognosis, Outcome prediction

Introduction

Patients with severe infections and presumed sepsis account for a considerable group of patients admitted to an emergency department (ED [1]. The prevalence of patients with sepsis and severe sepsis or septic shock presenting at the ED was observed in 2.1 to 6.3% and 0.6 to 0.9%, respectively [2]. Patients with early sepsis and evolving severe sepsis or septic shock should already be identified at first presentation because delay in antibiotic administration is associated with increased in-hospital mortality, whereas early goal-directed therapy for the treatment of severe sepsis and septic shock initiated in the ED may reduce mortality [3, 4].

Currently, the most commonly used biomarkers are C-reactive protein (CRP) and procalcitonin (PCT), but these markers have failed to be useful for individual prognostic stratification and for identification of those patients with early sepsis who are at high risk of developing severe sepsis or septic shock.

Apart from CRP and PCT, which are synthesized during inflammation and infection, markers of neutrophil and monocyte activation have been investigated as potential biomarkers of sepsis including the membrane bound protein CD14, a 55 kDa membrane glycoprotein which is anchored to the cellular membrane of monocytes, macrophages, and granulocytes through a glycosyl phosphatdylinostol linkage. Upon monocyte activation, CD14 is shed from the cell membrane and circulates as soluble CD14 (sCD14), which exists in two molecular forms (55 kDa and 49 kDa). During activation and shedding of CD14 from the cell surface membrane, one molecule sCD14 is split into approximately four molecules of the 13 kDa fragment sCD14-ST [5].

A chemiluminescent immunoassay using a specific antibody to determine sCD14-ST, named PSEP, is commercially available. First results of clinical studies

using this assay showed higher concentrations of PSEP in patients with sepsis than in healthy controls and in patients with systemic inflammatory response syndrome (SIRS) [6]. PSEP concentrations correlated with the severity of sepsis and outcome, suggesting that PSEP may be a promising biomarker and indicator of systemic infections or sepsis and a marker candidate for prognosis and therapy monitoring [7-9]. Additionally, a recent multicenter trial demonstrated a high prognostic value of PSEP for mortality prediction in patients with severe sepsis and septic shock. This finding could not be confirmed for procalcitonin (PCT) [10].

2. Materials and Methods

The study was performed as a single-center, prospective observational study including consecutive emergency patients admitted to the ED of the Hospital Nacional Edgardo Rebagliati Martins - EsSalud, Lima, Peru between November 2012 and February 2013. The study was approved by the local ethics committee. All patients provided informed consent prior to enrollment.

2.1 Study population

One hundred twenty-three adult patients (> 18 y) with suspected sepsis were included in the study. Sepsis was diagnosed if at least 2 criteria for SIRS (body temperature > 38°C or < 36°C, heart rate > 90 min-1, respiration rate > 20 min-1 or hyperventilation (PaCO2 < 4.3 kPa), leukocytosis (> 12000 mm-3) or leucopenia (< 4000 mm-3) or > 10% premature granulocytes) were present and there was proven infection or strong suspicion based on clear clinical signs. Patients who had received

antibiotics during the 72 h prior to entering the ED were excluded. Sepsis, severe sepsis, and septic shock were defined according to the guidelines of the American College of Chest Physicians / Society of Critical Care Medicine Consensus Conference [11]. The MEDS score was assessed at first presentation. To describe disease severity, the Acute Physiology and Chronic Evaluation (APACHE II) score was assessed 24 and 72 h after hospital admission.

2.2 Outcome

The primary endpoint was death within 30 days after admission. Secondary endpoints were transfer to an intensive care unit (ICU), need for mechanical ventilation and need for the initiation of dialysis. The combined endpoint consisted of either the primary or at least one of the secondary endpoints. Occurrences of any endpoints were evaluated until day 30 after hospital admission.

2.3 Control group

One hundred twenty-three healthy volunteers (31 females and 92 males, aged 18 to 56 y, mean 35 y) who served as blood donors at the service center for transfusion medicine of the hospital Edgardo Rebagliati Martins – EsSalud formed the control group for determination of the reference interval of PSEP.

2.4 Sampling and laboratory analysis

EDTA plasma samples were collected at admission to the ED. Additional plasma samples were obtained 8, 24 and 72 h later, after admission to the general ward or ICU. The plasma samples were stored at -70°C until measurement.

PSEP was determined using PATHFAST PSEP (Mitsubishi Chemical Medience), a chemiluminescent enzyme immunoassay for the quantitative measurement of PSEP concentration in whole blood or plasma. The test principle is based on the non-competitive chemiluminescence enzyme immunoassay (CLEIA) combined with *MAGTRATION® technology [12]. During incubation of the sample with alkaline phosphatase-labeled anti-PSEP polyclonal antibody and anti-PSEP monoclonal antibody-coated magnetic particles, PSEP of the sample binds to the anti-PSEP antibodies, forming an immune-complex with enzyme-labeled antibody and antibody-coated magnetic particles. After removal of the unbound substances by *MAGTRATION® technology, a chemiluminescent substrate is added. After a short incubation period, the luminescence intensity generated by the enzyme reaction is measured. The luminescence intensity is related to the PSEP concentration of the sample, which is calculated by means of a standard curve (measurement range: 20 – 20000 ng/l, functional sensitivity: 57.1 ng/l, reference interval: 60 – 365 ng/l).

2.5 Statistical analysis

Results of PSEP determination were summarized calculating median values and their respective 95 % confidence intervals (CI) or interquartile ranges (IQR) and were compared using a two-sided *t*-test or Welch test for equal and unequal variances (which was first determined using the F-test). Categorical variables were compared using a frequency table or the chi-square or Fisher's exact test. A logistic

regression model was used to identify independent predictors of mortality and included log-transformed concentrations of PSEP. Receiver operator curves (ROC) were generated to determine cutoff values for defined diagnostic specificities. Kaplan-Meier survival analyses were performed to show the prognostic power of PSEP concentration with respect to 30-day mortality. The results of comparisons were reported accepting a p-value < 0.05 as significant. All calculations were carried out using MedCalc® Version 9.3.5.0.

2.6 Sample size calculation

The sample size needed to meet the objectives of this study was calculated with PASS 11 statistical software (Power Analysis and Sample Size) - NCSS - LLC, with a statistical power of 0.8, a reliability coefficient of 0.05 and considering an initial correlation of our data of 0.4 and a minimum expected correlation of 0.6, the number of subjects to be included in our research would be 111; however, allowing for a loss in monitoring and errors in information recollection of 10%, the final sample size is 123 subjects. According to CLSI guidelines for determining reference values of a new marker it is necessary to have 120 healthy subjects; we therefore recruited a total number of 123 subjects.

3. Results

3.1 Reference interval of PSEP

The PSEP concentrations measured in EDTA plasma samples obtained from 123 healthy volunteers revealed a PSEP range of 58 to 339 ng/l and a 95% reference interval based on normal distribution according to CLSI C28-A3, with an upper and lower reference limit of 236 ng/l (90% CI: 222 – 250 ng/l) and 24 ng/l (90%

CI: 10 – 38 ng/l) respectively. Males showed slightly higher values than females. Median values were 133 and 101 ng/l respectively (p=0.0435). Median PSEP concentrations of the control group were 123 (IQR: 89-155) ng/l compared with 804 (IQR: 416-2255) ng/l of the patients with sepsis (n=114) at admission to the ED.

3.2 Baseline laboratory and clinical characteristics of the study population

The final diagnosis was SIRS, sepsis, severe sepsis and septic shock in 9, 74, 34 and 6 patients respectively. The baseline clinical and laboratory characteristics of the patients, including medical history and infective foci, are displayed in Table 1. The infective foci were identified by clinical signs and symptoms. The most frequent infective foci in the total study group were urinary tract (34.1%), lung (30.7%) and abdomen (20.1%), whereas in patients with severe sepsis or septic shock and in decedents, respiratory tract infections showed the highest frequency at 37.5% and 58.3%.

Table 2 shows a comparison of the clinical conditions in survivors and non-survivors. A medical history of stroke and kidney diseases was present in 15.2% and 14.1% of the survivors, whereas the frequency of these conditions was 25% and 29.1% in decedents, followed by fibrosis of the lung (16.7%). In contrast, only 1 patient died out of 16 patients with a history of diabetes mellitus.

The results of sub-population analysis for PSEP concentration at admission are displayed in Table 3. The patients with a medical history of kidney disease revealed noticeably higher PSEP concentrations. Median values in patients with a history of kidney disease were 6056 (IQR: 2518-8674) compared to 690 (IQR: 395-1971) ng/l in the patients of the total study population (n=123). Similar ratios were

found in survivors (n=13) and non-survivors (n=7) of the patients with a medical history of kidney disease.

3.3 Discrimination between SIRS, sepsis, severe sepsis and septic shock

PSEP at admission (0 h) exhibited a significant difference between healthy controls, patients with SIRS, sepsis and severe sepsis or septic shock reaching a significance level of $p<0.0001$ (Fig. 1). At the measurements after 8 h, 24 h and 72 h, PSEP also differed significantly between the patient groups (see Tab. 1).

The discriminatory power of PSEP for differentiation between SIRS and sepsis at admission to the ED was examined by ROC analysis in comparison with the MEDS score. ROC analysis revealed an optimized cutoff value of 581 ng/l for PSEP, with sensitivity and specificity of 65 % and 100 % respectively. The area under the curve (AUC) was 0.83 (95% CI: 0.751-0.891). The corresponding AUC of the MEDS score was 0.91 (95% CI: 0.845-0.945), with sensitivity and specificity of 61% and 100 %. Simultaneous assessment of PSEP and MEDS score revealed an improved discriminatory power, reaching an AUC of 0.95 (95% CI: 0.894-0.981), with sensitivity and specificity of 85 % and 100 %.

3.4 Risk of mortality and outcome prediction

In summary, 24 patients died and 35 patients reached the combined endpoint during the 30-day follow-up. The number of decedents and patients who reached the combined endpoint were 7 (9.5%) / 11 (14.9%), 14 (41.2%) / 19 (55.9%) and 3 (50%) / 5 (83.3%) in patients with sepsis (n=74), severe sepsis (n=34) and septic shock (n=6) respectively. The diagnoses and outcomes of survivors and non-survivors of the entire study population were analyzed. The results are shown in Table 2. PSEP

as well as the MEDS score differed significantly between survivors and non-survivors. Median values of PSEP at admission in survivors and non-survivors were 590 (IQR: 345-1396) ng/l and 1793 (IQR: 705-6616) ng/l respectively. Quartiles of PSEP showed a strong correlation ($p<0.0001$ for trend analysis) with the risk of 30-day mortality, ranging from 10.7% in the 1st to 32.4% in the 4th quartile. ROC analyses were performed comparing the accuracy of the prediction of 30-day mortality and combined endpoint of PSEP and MEDS score (Fig. 2). PSEP demonstrated comparable prognostic accuracy. The results of the Kaplan-Meier survival analysis using the ROC optimized cutoff value for baseline PSEP (> 825 ng/l) are shown in Fig. 3.

3.5 Disease monitoring

All study patients received antibiotic or anti-infective therapy at admission when the clinical diagnosis of sepsis was established. To investigate the ability to determine the efficacy of initial therapeutic measures at a very early stage, we evaluated the course of PSEP concentrations measured at presentation, and 8, 24 and 72 hours after admission. In the survivors (n=99), the median values remained below 600 ng/l and showed a decreasing tendency from baseline to 72 hours. In the non-survivors (n=24), the median values were significantly higher (> 1700 ng/l) and showed an increasing tendency. This effect became clear from the course of the median values and 95% confidence intervals, as displayed in Figure 4.

4. Discussion

Despite advances in clinical research during the past decades and growing compliance with the recommendations and guidelines of the Surviving Sepsis

Campaign for the management of septic patients [13,14], sepsis still remains a potentially lethal complication. In addition, the incidence of sepsis has doubled during the past decade, in line with the increasing age of hospitalized patients and increasing admittance of outpatients suspected of sepsis to the emergency department (ED) [15]. Sepsis, severe sepsis and septic shock represent the most common complications in patients in the ED and the intensive care unit (ICU). Despite modern antibiotic therapy and additional cardiovascular, kidney function-related and respiratory measures, the mortality rate remains unacceptably high (16). The early recognition of sepsis and identification of patients who develop severe sepsis or septic shock and worse outcome at the time of first presentation in the ED could significantly improve the therapeutic management of sepsis (17). Nonetheless, early risk stratification and monitoring clinical treatment still remain unsolved. At present the assessment of diagnosis or prognosis as well as the monitoring of sepsis with circulating biomarkers rely on PCT. However, despite the widespread clinical implementation as diagnostic marker for systemic bacterial infection, PCT has shown limited value for risk stratification and prognostication of sepsis (18).

In this prospective study we investigated the diagnostic and prognostic power of PSEP in patients suspected of sepsis presenting in the ED and during the first 3 days of hospitalization. Final diagnoses were based on the criteria of the International Guidelines for Management of Severe Sepsis and Septic Shock (3). The study population consisted of patients with SIRS (n=9) due to acute pancreatitis but without evidence of infection, patients with sepsis (SIRS and infection, n=74), severe sepsis (sepsis and organ failure, n=34), and septic shock (multi-organ failure and refractory hypotension, n=6). Alternatively, patients with severe sepsis and septic shock were subsumed under one group for specific statistical considerations, as these conditions

exhibited similar clinical situations. Additionally, healthy volunteers served as a control group.

Only few data about PSEP concentrations in a reference population are available. Two recent studies reported PSEP concentrations measured in heparinized plasma samples obtained from obviously healthy individuals. 127 controls of healthy patients revealed a concentration range of 92.7 to 398 ng/l, an arithmetic mean of 189 ng/l, and 5th and 95th percentile values of 105 and 333 ng/l (19). A study including 70 healthy controls reported a mean value of 259 ng/l and a concentration range between 111 and 425 ng/l (20). The manufacturer indicated an upper reference limit of 320 ng/l (21). In our study, PSEP values of the healthy control group ranged from 58 to 339 ng/l, the 5th and the 95th percentile values were 61 and 230 ng/l, the arithmetic mean value was 130 ng/l. Regarding these inconsistencies viewed in the context of the high medical relevance of the early recognition of sepsis, the reference interval of PSEP should be established multicentrically according to the CLSI standard procedures.

Median PSEP concentrations at presentation in the ED differed highly significantly between healthy controls (123 ng/l) and patients, as well as between SIRS (304) and the different severity degrees: sepsis (544 ng/l), severe sepsis or septic shock (2037 ng/l). The results were comparable to those reported by Liu et al. (8) and Kweong et al. (24), but differed from Ulla et al. (7), who reported significantly higher PSEP concentrations in patients with SIRS and the severity degrees of sepsis as well. The differentiation between SIRS and sepsis at presentation in the ED was examined by ROC analysis and demonstrated a high discriminatory power (AUC=0.829), Sensitivity 61%, specificity 100% at a PSEP threshold of 581 ng/l. This result suggests that the PSEP concentration is already related to the severity of the

disease at the time of first presentation and may be useful in the differential diagnosis in patients presenting with clinical signs of SIRS and sepsis in the ED. In summary, based on the PSEP values measured in the study patients with different disase severity degrees (SIRS, sepsis, severe sepsis or septic shock) and the close relationship between PSEP and outcome (30-day death or combined endpoint) decision thresholds for risk stratification could be established: <200 pg/mL: very low risk), >300 pg/mL: moderate risk, > 500 pg/mL; high risk, and > 1000 pg/mL: very high risk (Table 4).

The data underline the finding of another study that PSEP may differentiate SIRS patients with bacterial infection from those without (9).

Sub-population analysis showed no significant correlation between the different populations, except in patients with a history of kidney disease and patients with a central venous catheter (CVC) as infective focus. Although PSEP concentrations did not correlate significantly with the focus of infection, CVC-related infections showed a significantly higher median value of 5714 ng/l compared to 522, 596, 673 and 773 ng/l in skin, lung, abdomen and urinary-tract-related infections respectively. The most frequent disease in medical history was stroke. The highest mortality was found in patients with a history of stroke and kidney diseases, followed by fibrosis of the lung and liver-related diseases. Regarding the site of infection, the highest mortality was exhibited by patients with lung or respiratory-tract-related infections.

The noticeably higher PSEP values in patients with a history of kidney disease as indicated in Tab. 3 give reason to assume that PSEP plasma concentration is associated with renal function. PSEP as a 13 kDA protein is filtered by the

glomerulus and reabsorbed within proximal tubular cells. Thus, decreasing kidney function should cause accumulation of PSEP in the circulation, resulting in elevated plasma PSEP concentration. Kidney injury and renal dysfunction occur commonly in septic patients. In particular, sepsis may induce deterioration of renal dysfunction in patients suffering from chronic kidney disease. This could be underlined by the coefficient of correlation between PSEP and creatinine of 0.6643 ($p<0.0001$) in the septic patients of the study population. Remarkably, all patients with CVC had chronic kidney disease and were on haemodialysis which might be the reason for the high PSEP concentrations observed in these patients . In this study, PSEP thresholds have been established for the discrimination between SIRS, sepsis, severe sepsis or septic shock and for outcome prediction. Sub-population analysis revealed that these thresholds cannot be applied to patients with a medical history of kidney disease. Failure to excrete PSEP through the kidney remains one possible explanation for the observed effect. Other factors require consideration, such as chronic inflammation in chronic renal disease, diseases predisposing to chronic renal failure such as diabetes mellitus, predominantly type 1, or consequences of chronic renal failure such as heart failure. These questions need to be addressed in future studies. Another aspect is the use of PSEP in patients with chronic renal failure for diagnostic or prognostic purposes. Currently established PSEP thresholds cannot be used in this population and further studies including control groups with chronic renal failure without evidence of infection need to be initiated. These studies should also address the question of acute or chronic renal failure and corresponding PSEP concentrations in urine in different clinical situations. Such studies could additionally evaluate the diagnostic and prognostic validity of PSEP in patients on chronic dialysis.

We investigated the potential prognostic power of PSEP at presentation in an ED setting and during the hospital stay in patients with sepsis, severe sepsis and septic shock. A recent study of patients presenting at the ED with suspected sepsis or septic shock showed that PSEP concentration at presentation was associated with 60-day mortality (7). A case-control study of a multicenter clinical trial enrolling patients with severe sepsis or septic shock showed that early PSEP was significantly higher in decedents than in survivors, while PCT was not (10). The evolution of PSEP concentrations over time was significantly different in survivors compared to non-survivors, while PCT decreased similarly in the two groups. This finding confirmed comparable results of a former study showing that PSEP values in survivors and decedents differed significantly during the first 72 hours. The PSEP values increased in decedents, whereas the values decreased in survivors (22). In the present study, PSEP concentrations at admission to the ED showed a close correlation with disease severity and 30-day mortality, suggesting that PSEP may be useful for early recognition of evolving organ failure and mortality prediction at the first presentation in the ED. This finding corresponds to the concept that an increasing degree of evolving severity during the course of sepsis increases the risk of death (23). Additionally, our findings demonstrated that simultaneous assessment of PSEP and MEDS score at the time of first presentation facilitated discrimination between SIRS and sepsis and improved mortality prediction (Fig. 2).

All study patients received antibiotic or anti-infective therapy at admission when the clinical diagnosis of sepsis was established. PSEP values measured at presentation, at 8, 24 and 72 h after admission were statistically evaluated to investigate the ability to determine the efficacy of initial therapeutic measures at a very early stage. The PSEP concentrations were significantly lower in survivors than

in decedents and remained at the low concentration during the observation time of 72 h. Although the study design is not suitable to prove any direct association between the antibiotic treatment and the course of PSEP, it may be assumed that lower PSEP concentrations with a decreasing tendency can be associated with a beneficial effect of the treatment.

5. Limitations

The study included only 9 patients with SIRS suffering from pancreatitis. It would be preferable to include a higher number of SIRS patients with diseases other than pancreatitis in addition in order to obtain a more reliable result for the discrimination between SIRS and sepsis by means of the biomarker PSEP. The biomarkers PCT, CRP or interleukin-6 which are actually used in the diagnosis of sepsis were not determined in the study. Therefore the performance of PSEP could not be compared directly, but only with results from literature. A minor limitation is that the infective foci were identified by clinical signs and symptoms without the use of microbiological tests.

6. Conclusion

Our findings indicate that PSEP may be a promising early diagnostic and prognostic marker in septic patients. ROC analysis revealed that PSEP allowed early risk prediction of mortality and adverse outcome at the time of admission. Furthermore, PSEP values in the course of the disease differed between non-survivors and survivors, suggesting that PSEP might be suitable for monitoring therapeutic measures. In summary, disease conditions with increased concentrations of PSEP concentration were associated with increased mortality. PSEP appeared to be an accurate diagnostic marker for differentiation between SIRS and sepsis as well

as between sepsis severity grades, prediction of outcome and risk of mortality. PSEP as a single marker value provides similar information as MEDS or APACHE II score which represent compositions of different criteria which are to be collected by the emergency physician. Contrary to this, PSEP values can be obtained from whole blood at presentation within 15 min by using the POC system PATHFAST™ without time delay. Moreover, our data showed that the simultaneous assessment of PSEP and MEDS score improved discrimination of severity degrees as well as mortality and outcome prediction.

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Figure Legends

Figure 1: PSEP concentrations in healthy controls and in patients at admission to the ED

Figure 2: Simultaneous assessment of PSEP and MEDS score at admission for mortality prediction and discrimination between SIRS and sepsis

– A: ROC curves for discrimination between SIRS and sepsis; B: ROC curves for prediction of 30-day death

Figure 3: Kaplan-Meier survival curve of 30-day death for PSEP at admission

Figure 4: PSEP in the course of the disease (median values and 95% CIs) in non-survivors (red) and survivors (blue)

Table 1: Characteristics of the study group

		Total	SIRS	Sepsis	Severe sepsis Septic shock
		n=123	n=9	n=74	n=40
Demography					
	Age; median(min-max)	67(21-95)	34(27-64)	69(24-94)	70(21-95)
	Male; %	45.5	22.2	41.9	57.5
Medical history					
	Stroke; n, *%*	21, *17.1*	0, *0*	15, *20.3*	06, *15.0*
	Diabetes; n, *%*	15, *12.2*	0, *0*	12, *16.2*	03, *07.5*
	Kidney diseases; n, *%*	20, *16.3*	0, *0*	8, *10.8*	12, 30.*0*
	Lithiasis; n, *%*	12, *9.8*	5, *44.4*	4, *5.4*	3, *7.5*
	Liver disease; n, *%*	7, 5.7	0, *0*	2, *2.7*	5, *12.5*
	Fibrosis of the lung; n, *%*	7, 5.7	0, *0*	4, *5.4*	3, *7.5*
	Others, n, *%*	9, *7.3*	1, *11.1*	4, *5.4*	4, *10.0*
Infective focus					
	Urinary tract; n, *%*	42, *34.1*	0, *0*	33, *44.6*	9, 22.*5*
	Lung; n, *%*	35, 30.7	0, *0*	20, *27.0*	15, *37.5*
	Abdomen; n, *%*	23, *20.1*	0, *0*	14, *18.9*	9, 22.*5*
	Central venous catheter; n, *%*	5, *4.4*	0, *0*	2, *2.7*	3, *7.5*
	Skin; n, *%*	5, *4.4*	0, *0*	4, *5.4*	1, *2.0*
	Others, n, *%*	4, *3.5*	0, *0*	1, *1.4*	3, *7.5*
MEDS	0 h; median (95% CI)	5 (3-6)	0 (0-3)	3.5 (3-6)	8 (6-10)
APACHE II	24 h; median (95% CI)	13 (10-15)	3 (2-4)	11 (9-12)	18 (15-21)
	72 h; median (95% CI)	9 (9-11)	2(0-3)	8 (6-9)	16 (13-18)
PSEP (ng/l)					
	0 h; median (95% CI)	690 (556-955)	304 (175-477)	544 (457-688)	2037 (1482-3668)
	8 h; median (95% CI)	700 (563-1014)	320 (184-635)	536 (453-706)	2134 (1403-4119)
	24 h; median (95% CI)	637 (538-886)	260 (214-333)	572 (450-657)	2428 (1252-4334)
	72 h; median (95% CI)	623 (475-888)	244 (158-830)	472 (391-596)	2020 (1037-5109)
Outcome					
	30-days death; n, *%*	24, *19.5*	0, *0*	7, *9.5*	17, *42.5*
	Combined endpoint; n, *%*	35, *28.5*	0, *0*	11, *14.9*	24, *60.0*

Table 2: Baseline clinical characteristics in survivors and in non-survivors

		Survivors n=99	Non-survivors n=24	
Demography				p-value
	Age; median(min-max)	65 (24-95)	75 (21-94)	0.0674
	Male; %	45.8	54.1	n.s.
Medical history				
	Stroke; n, *%*	15, *15.2*	6, *25.0*	n.s.
	Diabetes; n, *%*	14, *14.1*	1, *4.2*	n.s.
	Kidney diseases; n, *%*	14, *14.1*	7, *29.1*	n.s.
	Lithiasis; n, *%*	11, *11.1*	0, *0.0*	n.s.
	Liver disease; n, *%*	4, *2.7*	3, *12.5*	n.s.
	Fibrosis of the lung; n, *%*	3, *3.0*	4, *16.7*	n.s.
	Others, n, *%*	7, *7.1*	3, *12.5*	n.s.
Infective focus				
	Urinary tract; n, *%*	38, *38.4*	4, 16.7	n.s.
	Lung; n, *%*	21, *21.2*	14, *58.3*	n.s.
	Abdomen; n, *%*	28, *28.3*	3, 12.*5*	n.s.
	Central venous catheter; n, *%*	4, *4.0*	1, *4.2*	n.s.
	Skin; n, *%*	5, *5.1*	0, *0.0*	n.s.
	Others, n, *%*	3, *3.0*	2, *8.3*	n.s.
MEDS score	0 h; median (95% CI)	3 (3-5)	10 (8-11)	<0.0001
APACHE II score				
	24 h; median (95% CI)	10 (9-12)	20 (18-23)	<0.0001
	72 h; median (95% CI)	7(6-9)	17 (14-22)	<0.0001
PSEP (ng/l)				
	0 h; median (95% CI)	590 (487-818)	1763 (819-5395)	0.0038
	8 h; median (95% CI)	622 (473-716)	1859 (1096-4785)	0.0005
	24 h; median (95% CI)	574 (471-712)	1731 (953-4149)	0.0033
	72 h; median (95% CI)	533 (429-697)	2056 (821-5450)	0.0013

Table 3: Sub-population analysis for PSEP concentrations at admission

	Total, n=123		Survivors, n=99		Non-survivors, n=24		
		PSEP (ng/l) Median (IQR) 690 (395-1971)		PSEP (ng/l) Median (IQR) 590 (345-1396)		PSEP (ng/l) Median (IQR) 1762 (705-6616)	
Medical history	**n**		**n**		**n**		**Mortality**
Stroke	21	442 (308-795)	15	401 (289-680)	6	811 (403-1368)	28.6%
Diabetes	15	834 (348-2540)	14	762 (303-2963)	1	852	6.7%
Kidney diseases	20	6056 (2518-8674)	14	4913 (2255-6716)	7	8224 (5331-9385)	35.0%
Lithiasis	11	1906 (330-3260)	11	1906 (330-3260)	0		9.1%
Liver disease	7	1808 (703-2037)	4	1259 (606-1991)	3	1808 (1162-10062)	42.9%
Fibrosis of the lung	7	487 (351-1525)	3	487 (359-835)	4	1086 (376-3650)	57.1%
Others	9	529 (293-814)	6	340 (242-751)	3	1356 (720-1992)	33.3%
Infective focus							
Urinary tract	42	773 (340-1269)	38	731 (340-1086)	4	1589 (849-4730)	9.6%
Lung	35	596 (401-1923)	21	494 (314-669)	14	1325 (689-5331)	40.0%
Abdomen	31	673 (380-2038)	28	601 (345-1995)	3	1808 (1162-7608)	9.7%
CVC	5	5714 (3265-10624)	4	4658 (2928-8435)	1	10446	20.0%
Skin	5	522 (430-3196)	5	522 (430-3196)	0	/	0.0%
Others	5	425 (282-3999)	3	425 (284-902)	2	6555 (297-12813)	40.0%

Table 4: Decision thresholds of PSEP for early risk stratification in patients with sepsis based on the study results

PSEP, ng/l	< **200**	**200**-300	**300**-500	**500**-1000	>**1000**
Risk status	**Very low**	**Low**	**Moderate**	**High**	**Very high**
Sepsis; n,%	6, ***8***	7, ***10***	22, ***30***	21, ***28***	18, ***24***
Severe sepsis/sept.shock; n,%	1, ***3***	1, ***3***	2, ***5***	6, ***15***	30, ***75***
30-day death; n,%	1, ***4***	1, ***4***	3, ***13***	5, ***21***	14, ***58***
Combined endpoint; n,%	2, ***6***	1, ***3***	4, ***11***	9, ***26***	19, ***54***

Figure 1

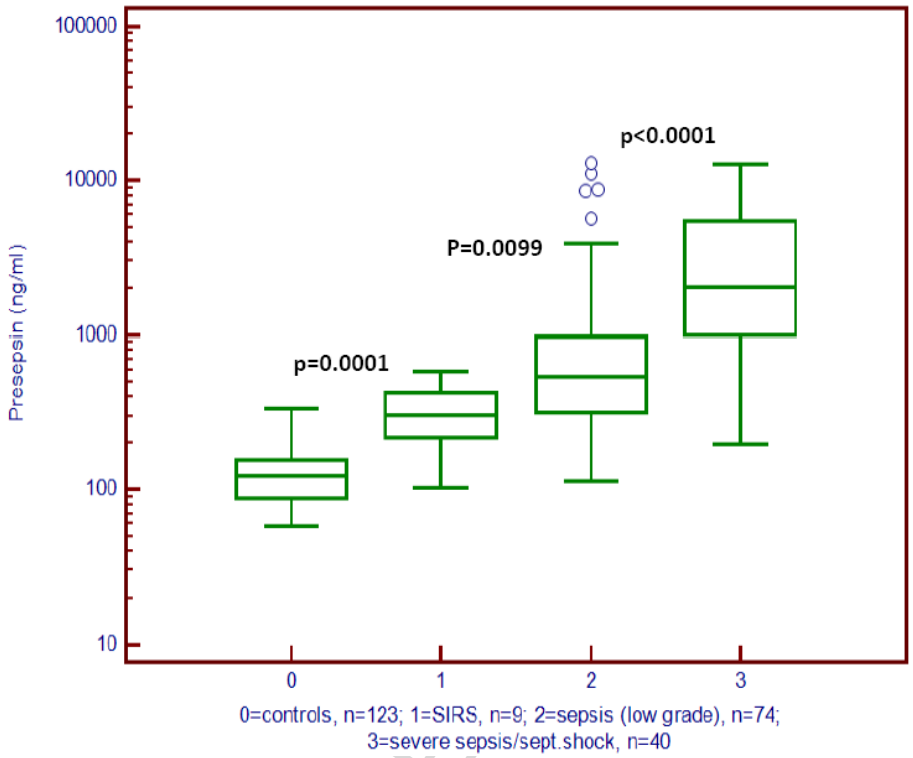
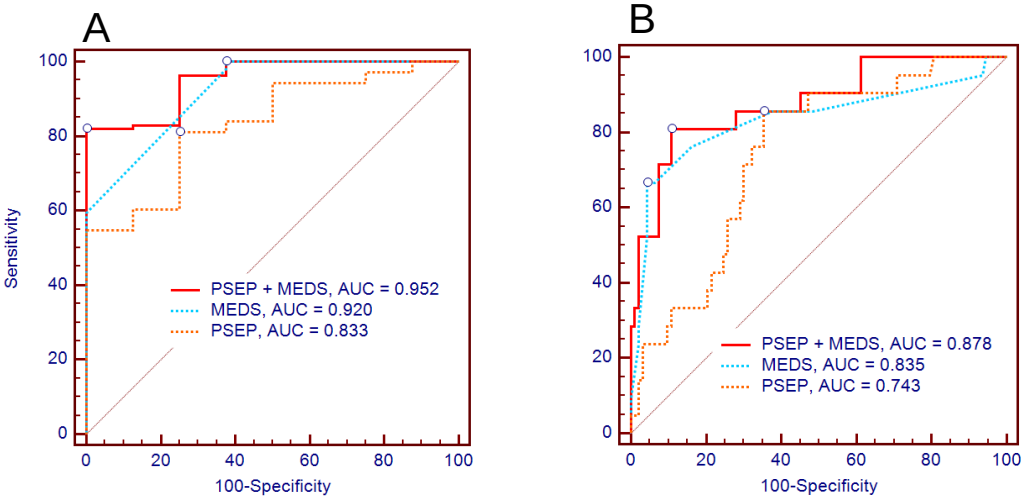


Figure 2



	SENS	SPEC	Cutoff
PSEP+MEDS	93%	100%	
MEDS	61%	100%	>3
PSEP	81%	75%	>370 ng/L

	SENS	SPEC	Cutoff
PSEP+MEDS	81%	89%	
MEDS	67%	93%	>3
PSEP	86%	65%	>825 ng/L

Figure 3

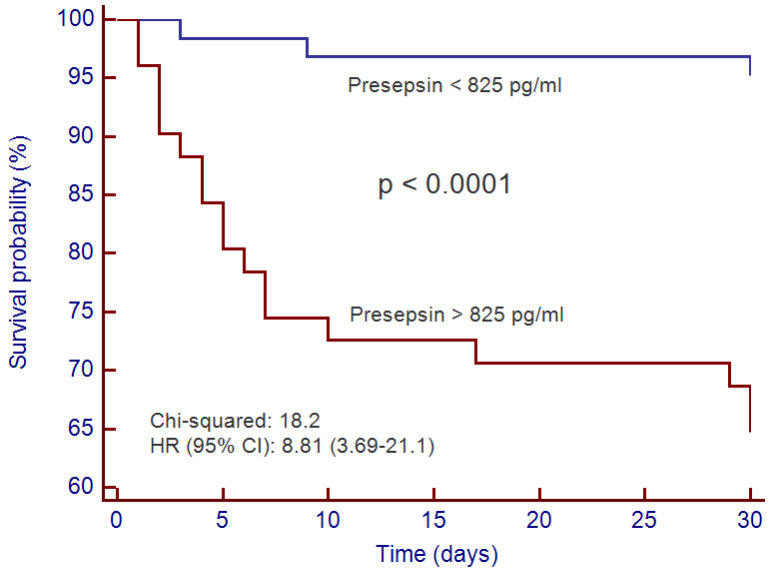
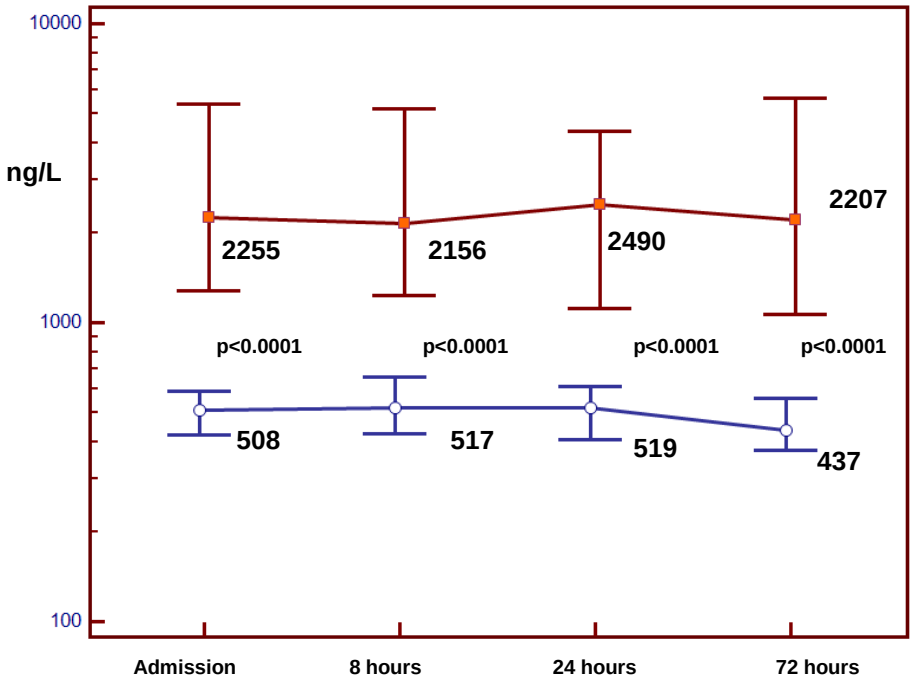


Figure 4



Medians and 95% CI: blue line: favourable outcome, n=77; red line: worse outcome (combined endpoint), n=37

Higlights:

- Presepsin levels differ significant between SIRS, sepsis, severe sepsis and septic shock.
- Presepsin is closely related to in-hospital mortality and short-term outcome already at first presentation in patients with sepsis.
- Simultaneous assessment of presepsin and clinical scores (MEDS, APACHE II) improves the prognostic power.
- Decision thresholds of presepsin for risk stratification in patients suspicious for sepsis were established.