Diagnostic and Prognostic Value of Soluble CD14 Subtype (sCD14-ST) in Emergency Patients with Early Sepsis Using the New Assay PATHFAST Presepsin

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Background: Soluble CD14 subtype (sCD14-ST, presepsin) serves as a mediator of the response to lipopolysaccharid from infectious agents. First evidence suggested that presepsin may be utilized as sepsis marker. ***The aim of the study*** was to examine the diagnostic and prognostic validity of presepsin in emergency patients with sepsis.

Methods: 140 patients presenting at the emergency room (ER) were included. EDTA plasma samples were collected at first presentation, 24 hours, and 72 hours after admission, and were stored at -70° C until determination of PATHFAST Presepsin. 119 healthy volunteers served as control group. Primary endpoint was death within 30 days. The combined endpoint "major adverse event" (MAE) consisted of at least either the primary or at least one of the secondary endpoints intensive care, mechanical ventilation or dialysis.

Results

Reference values. Presepsin concentrations of the control group and the patient group are displayed in Tab. 1.

Diagnostiv validity. For discrimination between low grade sepsis and severe sepsis presepsin showed the highest significance level reaching $p < 0.0001$ that was superior to IL-6, C-reactive protein (CRP) and procalcitonin (PCT) and comparable to those of the clinical scores (Tab. 2). Similar results (data not shown) were obtained for discrimination between survivors (N=117) and non-survivors (N=23).

Prognosic validity. The 30-day mortality ranged from 2.7% to 39.4% between the 1st and the 4th quartile (Tab. 4). Presepsin demonstrated a stronger relationship with 30-day mortality than procalcitonin. Receiver operating curve analysis of presepsin, procalcitonin and APACHE II score revealed AUCs of 0.878 (95% CI: 0.801-0.934), 0.668 (95% CI: 0.570-0.757) and 0.815 (95% CI: 0.709-0.895), respectively (Fig. 3).

Disease monitoring. All patients received antimicrobial therapy. In patients without occurrence of MAEs within 30 days after admission (N=104) the both marker levels decreased from baseline to 72 hours in the majority of the patients. In the patient group who experienced MAEs (N=36), both markers showed an increasing tendency. This effect was more pronounced for presepsin (Fig. 2).

Summary.
Decision thresholds could be established for diagnostic differentiation of sepsis grades and mortality prediction in septic patients presenting at the ER (Tab. 3). The determination of presepsin at presentation allowed reliable risk stratification already at the earliest time point in patients suspicious for sepsis admitted to the ER. The course of presepsin concentration during antimicrobial therapy was related with patient`s outcome.

Tab. 1: Presepsin levels in 119 healthy individuals and 140 patients

	Healthy individuals	Patients with sepsis
Min – Max, ng/L	60.1 – 365.0	338 – 15757
Mean (95% CI), ng/L	159.4 (148.1 – 170.7)	2433 (1593 – 3272)
Upper Refence Limit	**280 ng/L**	non-parametric percentile method (CLSI C28-A3)

Tab. 2: Biomarkers and clinical scores at admission to the ER

	Low grade sepsis N=91		Severe sepsis N=55		
	Mean	**95% CI**	**Median**	**95% CI**	**P-value***
IL-6, pg/ml	125	80 - 213	265	113 - 790	0.0123
CRP, mg/dl	148.3	93.7 - 190.4	195.7	125.1 - 260.8	0.0315
PCT, ng/ml	1.44	0.66 - 2.24	3.05	1.74 - 8.47	**0.0065**
Presepsin, pg/ml	782	559 - 932	1407	989 – 1868	**<0.0001**
APACHE II	14	11 - 17	23	20 – 27	<0.0001
GCS	15	15 - 15	14	11.0 - 14.5	<0.0001
MEDS	8	6 - 9	11	9.5 - 14.5	<0.0001
SOFA	4	3 - 5	6	5 – 8	0.0005

Tab. 3: Presepsin decision thresholds
based on presepsin determination at admission to the emergency department in patients with low grade sepsis (n=85), severe sepsis (N=40), sepstic shock (n=15), and 30-day death (n=23)

Risk stratification	**Very low**	**Low**	**Moderate**	**High**	**Very high**
Presepsin (ng/L)	**< 200**	**200-300**	**300-500**	**500-1000**	**≥ 1000**
Low grade sepsis, n (%)	3 (**3.5**)	9 (**10.6**)	18 (**21.1**)	29 (**34.1**)	26 (**30.6**)
Severe sepsis ,n (%)	0	0	5 (**12.5**)	11 (**27.5**)	24 (**60.0**)
Septic shock, n (%)	0	0	0	4 (**26.7**)	11 (**73.3**)
30-day death, n (%)	0	0	0	5 (**21.7**)	18 (**78.3**)

Tab. 4: Quartiles of presepsin or PCT and mortality

Quartile	**1st**	**2nd**	**3rd**	**4th**
Presepsin (ng/L)	177 – 512	524 – 927	950 – 1810	1850 – 15757
Mortality (p<0.0001)	**2.7%**	**8.6%**	**17.1%**	**39.4%**
PCT (ng/ml)	0.10 – 0.38	0.39 – 1.73	1.76 – 7.0	8.1 – 292
Mortality (p=0.9816)	**26.7%**	**8.1%**	**8.3%**	**24.3%**

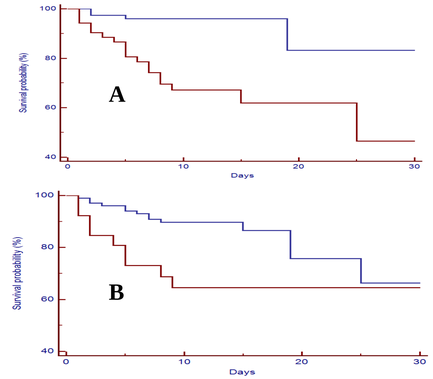

Fig. 2: **Kaplan-Meier survival curves for presepsin (A) and PCT (B)**

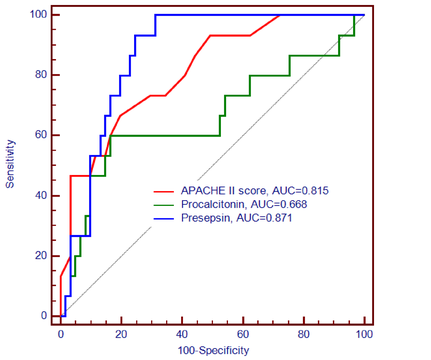

Fig. 2: ROC curves of presepsin, PCT and APACHE II score for predicting 30-day mortality

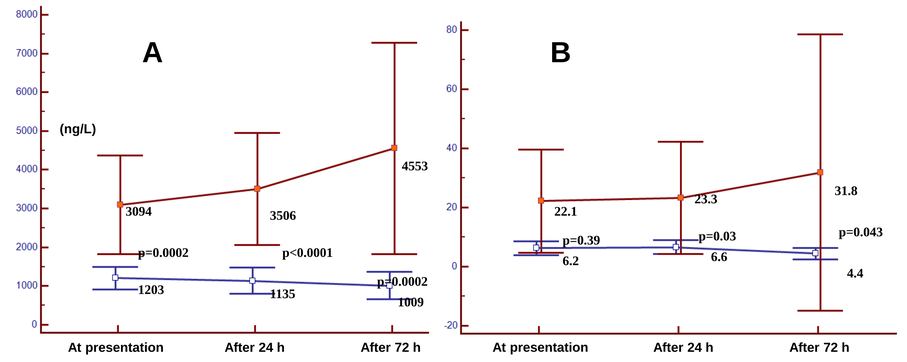

Fig. 2: Course of presepsin (A) and PCT (B) during microbial therapy in patients with worse outcome (red line, N=36) and favourable outcome (blue line, N=104)
(mean values, error bars: 95% CI)

Tab. 5: Improved risk prediction by combining clinical scores and presepsin
c-statistic and Net Reclassification Index (NRI)

	AUC alone	**AUC with presepsin**	**NRI**
APACHE II	0.815	0.905	54.38%
GCS	0.763	0.931	76.91%
MEDS	0.819	0.936	62.67%
SOFA	0.747	0.917	55.75%

Conclusion
These preliminary results suggested that presepsin is usable for early diagnosis and risk stratification of sepsis in the ER and therapy monitoring. Presepsin is superior in mortality prediction already at first presentation using the novel POC assay PATHFAST Presepin which allows reliable determination of presepsin within 17 min from whole blood samples in the ER.