PATHFAST Presepsin in patients with SIRS and early sepsis in the emergency department

Dr. Eberhard Spanuth
DIAneering® - Diagonstics Engineering & Research, Heidelberg, Germany

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Sepsis in the ED setting

- **~ 50% of all septic patients are initially seen in the ED.**
- **The patients are clinically heterogeneous. The condition is often difficult to recognize, especially in its early stages.**
- **In the ED many septic patients may be in an earlier state of the disease**.
- **and may be delayed there for hours before being transferred to a general ward or to an intensive care unit.**

Sepsis-related ED visits in the US

(National Hospital Ambulatory Medical Care Survey)

ED Disposition:	
Admitted to General Ward	75 %
Admitted to ICU	12 %
Other/missing	3 %
Discharged	10 %

Matthew C., et al. National Study of Emergency Department Visits for Sepsis. Ann Emerg Med 2006;48:326-331

Sepsis in the ED setting

- Only **8**% of all septic patients presenting at the ED are assigned to severe sepsis or septic shock.
- **30 – 40** % of patients with sepsis develop severe sepsis or septic shock with mortality rate > 30% during hospitalization.
- **60 – 70** % of the hospitalized septic patients may be assigned to "**uncomplicated sepsis**" with significant lower mortality rate (<10%).

Surviving Sepsis Campaign

Crit Care Med 2014 Aug;42(8):1749-55

Ferrer R, et al.: Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program.

In patients with severe sepsis and septic shock delay in first antibiotic administration was associated with increased in-hospital mortality.

In addition, there was a linear increase in the risk of mortality for each hour delay in antibiotic administration.

These results underscore the importance of early identification and treatment of high risk septic patients.

Sepsis in the ED setting

- For early goal directed treatment the therapeutic measures are normally not available in the ED.

- To decide whether a patient could be admitted to the general ward or must be admitted to the ICU the ED physicians need tools for rapid differentiation between septic patients with high mortality risk who develop severe sepsis or septic shock and those with „uncomplicated“ sepsis.

What is the medical and analytical need of a biomarker for sepsis?

Medical need:

1. A biomarker capable of detecting septic patients with elevated risk or developing severe sepsis would be a major asset!

2. A biomarker should be helpful in identifying septic patients who need more careful monitoring.

3. A biomarker should be capable of monitoring therapeutic measures.

Analytical need:

1. Rapid quantitative determination without time consuming sample processing

2. Easy handling at the POC

James Faix, MD, Stanford University: Biomarkers of sepsis. Crit Rev Lab Sci 2013;50:23-26

Presepsin in the ED setting

1. **ProFS** study
   (**Pro**gnose der **F**ruehen **S**epsis, *prognosis of early sepsis*)

   Study site: ED of the University Hospital Halle, Germany, 2010 - 2011

2. **SEED** study
   (**S**IRS and **E**arly Sepsis in the **E**mergency **D**epartment)

   Study site: ED of the Hospital Nacional Edgardo Rebagliati Martins-EsSalud, Lima, Peru, 2012 – 2013

Study design

Inclusion criteria:

- Clear signs or at least strong suspicion of infection
- Presence of at least 2 of 4 SIRS-criteria in a patient

Sample collecion:

ProFS: at first presentation in the ED, 24 hours, and 72 hours later

SEED: at first presentation in the ED, 8 hours, 24 hours, and 72 hours later

- **Both studies included a control group of healthy individuals**

Study design

Primary endpoint:

- Death within 30 days

Secondary endpoints:

- Mechanical ventilation
- Dialysis
- Intensive care

Combined endpoint:

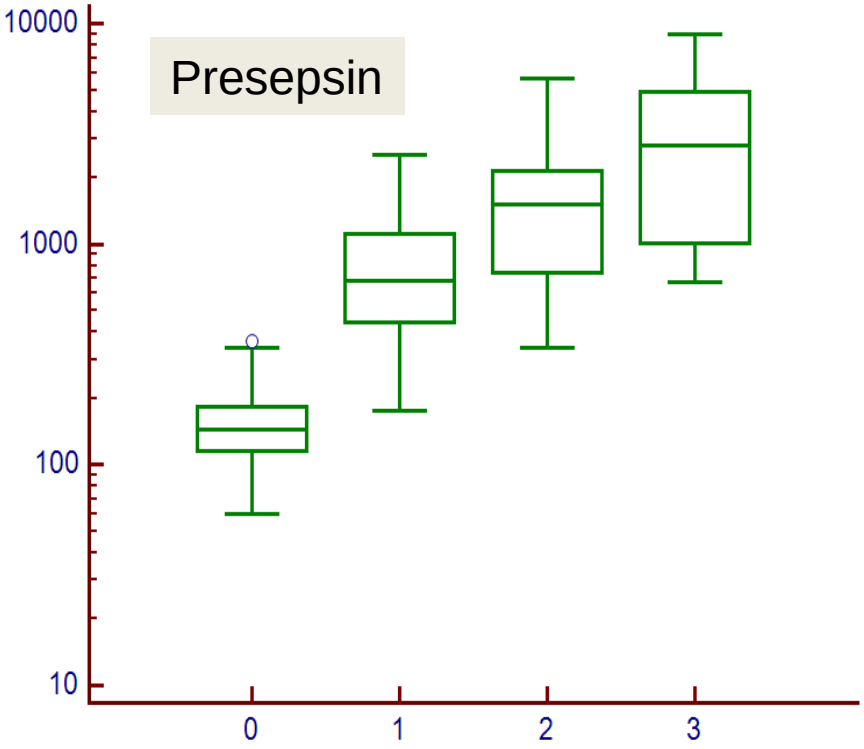
- At least one event (either the primary or at least one of the secondary endpoints)

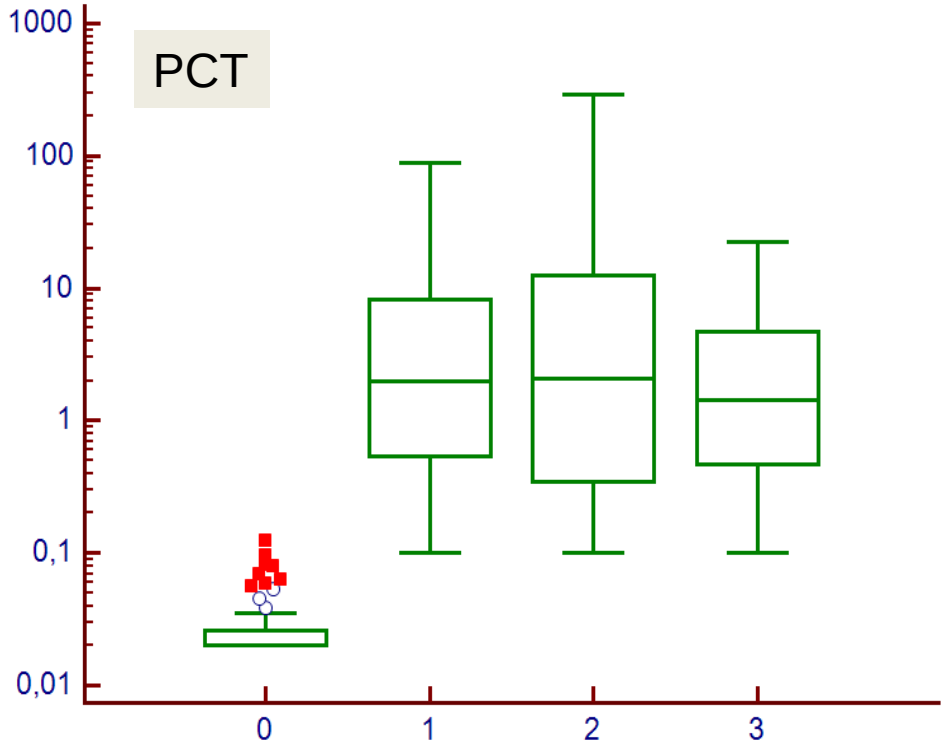
Presepsin in controls and septic patients

	Controls	Patients
ProFS, n **SEED**, n	119 123	140 123
Min – Max, ng/L ProFS SEED	 60 – 311 58 – 339	 338 – 15757 103 - 13036
Mean (95% CI) ProFS SEED	 148 (140 – 157) 130 (121 – 140)	 2563 (1458 – 3669) 1946 (1447 – 2445)
Upper Reference Limit (URL) ProFS SEED	 238 ng/L 243 ng/L	non-parametric percentile method (CLSI C28-A3)

ProFS study

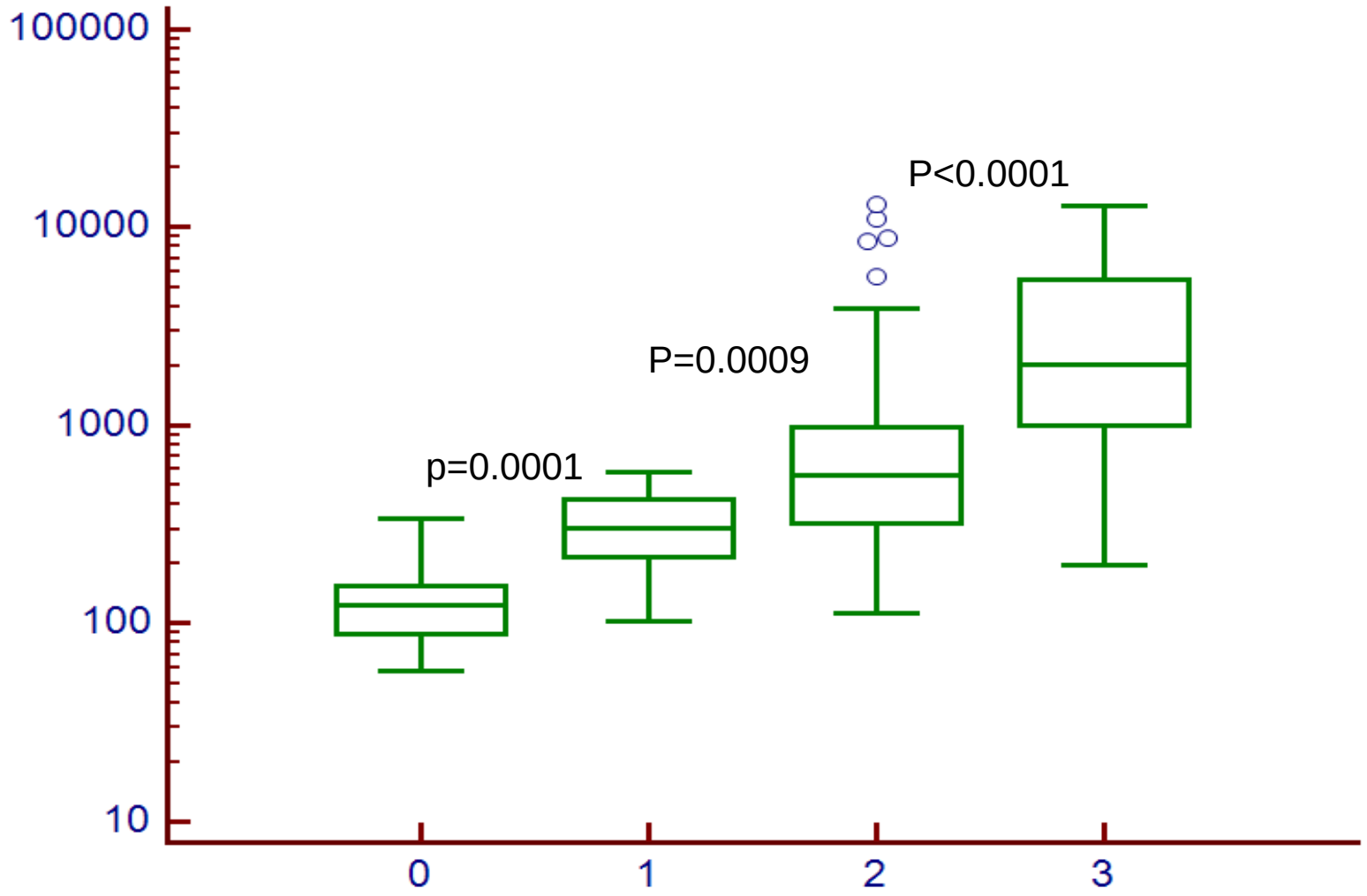
Presepsin and PCT in controls and septic patients ad admission





0 = controls (n=119), 1=sepsis (n=85), 2=severe sepsis (n=40), 3=septic shock (n=15)

SEED study: Presepsin ad admission in controls and septic patients



0 = controls (n=123), 1=SIRS (n=9), 2=sepsis (n=74), 3=severe sepsis or septic shock (n=40)

Primary endpoint death within 30 days

	Survivors	Non-Survivors
SIRS ProFS, n=0 SEED, n=9	 **0** **9**	 **0** **0**
Sepsis (uncomplicated) ProFS, n=85 SEED, n=74	 **82** **67**	 **3 (4%)** **7 (9%)**
Severe sepsis or septic shock ProFS, n=55 SEED, n=40	 **35** **23**	 **20 (36%)** **17 (43%)**

ProFS study

Relationship between marker concentration and mortality

Presepsin, ng/L Patients	**1. Quartile 177 – 512** n=37	**2. Quartile 524 – 927** n=35	**3. Quartile 950 – 1810** n=35	**4. Quartile 1859 – 15757** n=33
Survivors, n	**36**	**32**	**29**	**20**
Non-survivors, n	**1**	**3**	**6**	**13**
Mortality (%)	**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 (%)	**26.7**	**8.1**	**8.3**	**24.3**

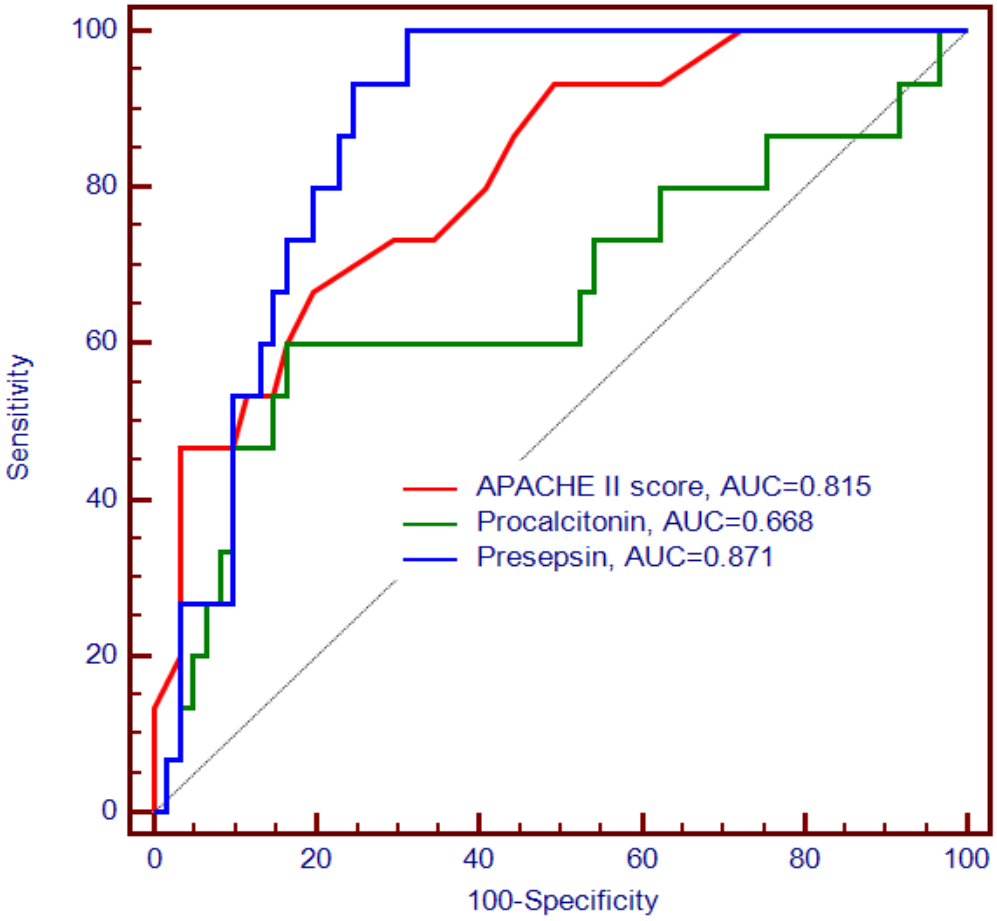
SEED study

Relationship between presepsin concentration and mortality

Presepsin, ng/L Patients, n	**1st Quartile 113 – 416 n=29**	**2nd Quartile 417 – 774 n=28**	**3rd Quartile 834 – 2255 n=29**	**4th Quartile 2436 – 13036 n=28**
Survivors, n	**26**	**24**	**21**	**19**
Non-survivors,	**3**	**4**	**8**	**9**
Mortality (%)	**10.3%**	**14.3%**	**27.6%**	**32.1%**

ProFS study

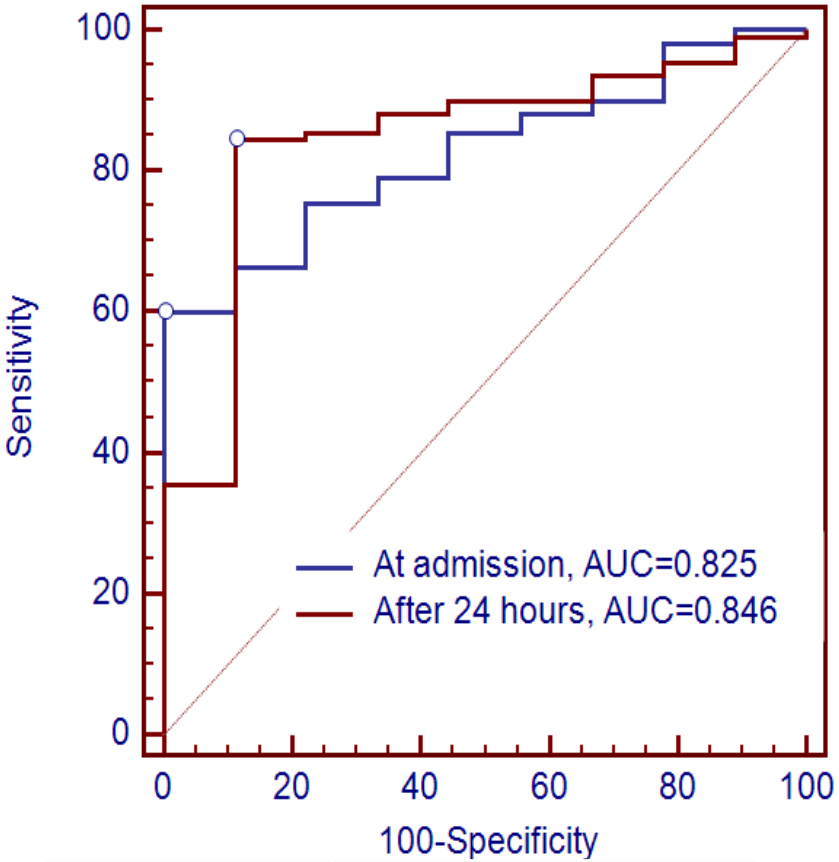
Results of ROC analysis for mortality prediction



APACHE II score, PCT, and presepsin at admission

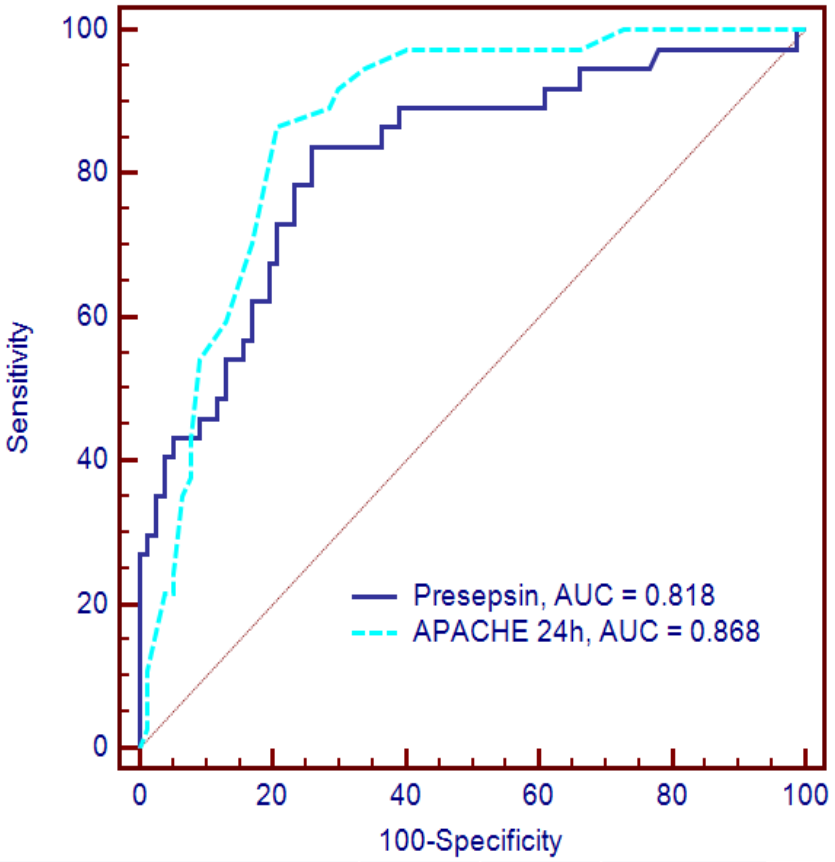
SEED study: results of ROC analysis

Discrimination between SIRS and sepsis



Presepsin	Sens (%)	Spec (%)	Cutoff, (ng/L)
At admission	60.5	100.0	581
After 24 h	84.5	88.9	336

Combined endpoint prediction

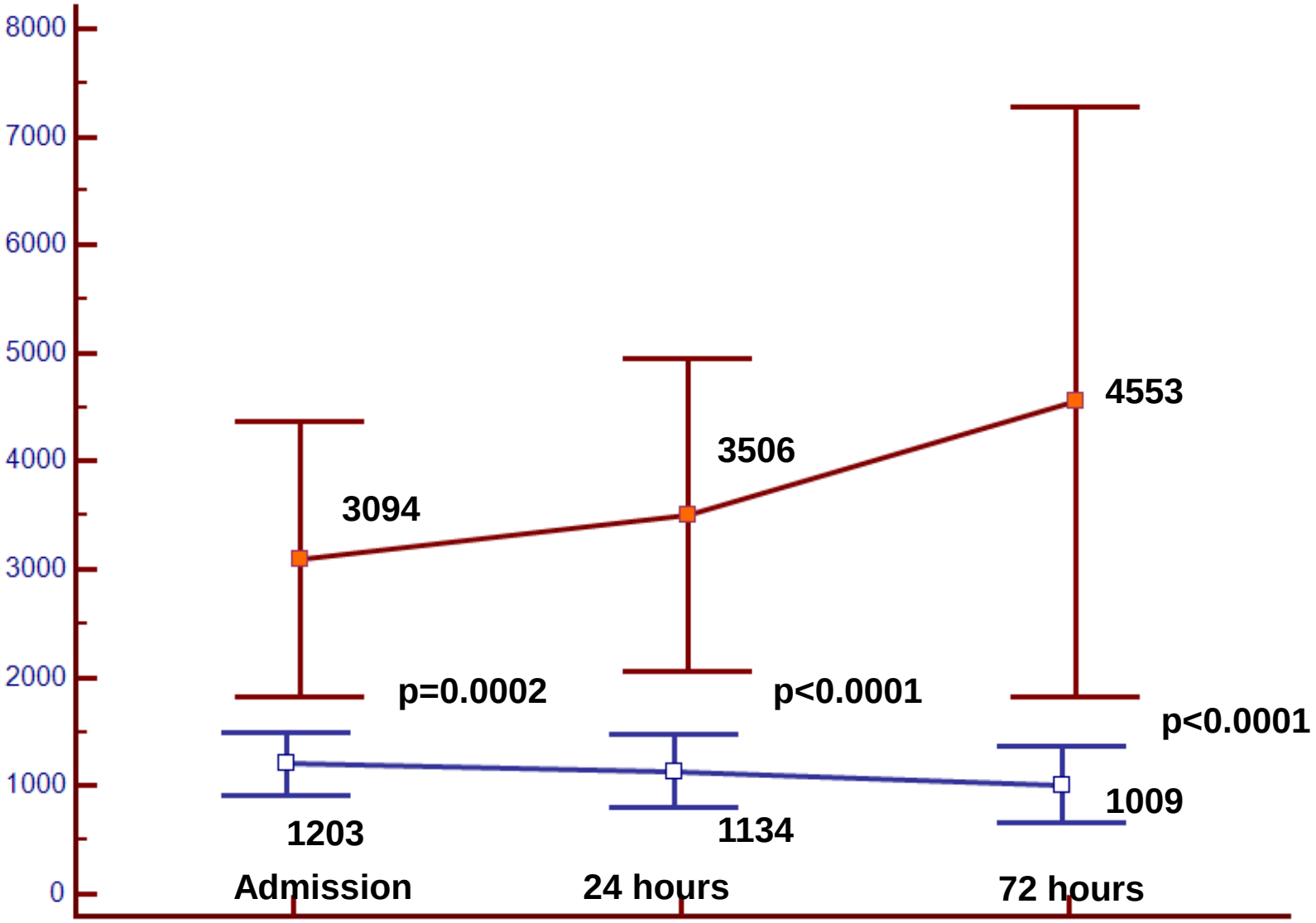


	Sens (%)	Spec (%)	Cutoff,
APACHE 24 h	87.8	79.3	14
Presepsin admission	83.8	74.0	825 ng/L

Presepsin decision thresholds for risk stratification and outcome prediction in the ED

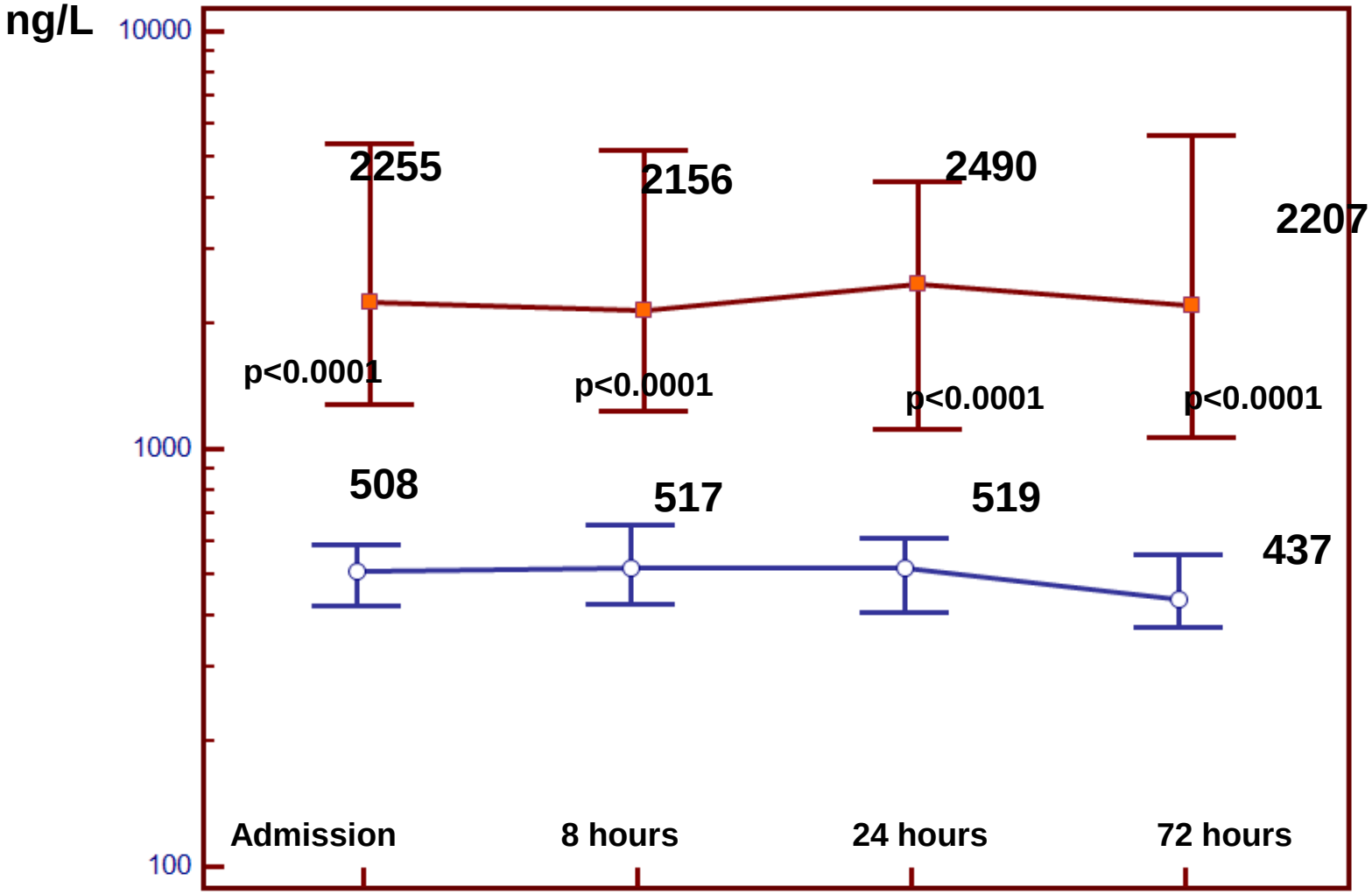
Risk	Low	Moderate	High	Very high
Presepsin, ng/L	**< 300**	**300-500**	**500-1000**	**≥ 1000**
Sepsis, n (%)				
ProFS	**8 (9.4)**	**22 (25.9)**	**29 (34.1)**	**26 (30.6)**
SEED	**6 (8.1)**	**24 (32.4)**	**26 (35.1)**	**18 (24.3)**
Severe Sepsis or septic shock, n (%)				
ProFS	**0 (0.0)**	**5 (12.5)**	**12 (21.8)**	**38 (69.1)**
SEED	**0 (0.0)**	**4 (10.0)**	**6 (15.0)**	**30 (75.0)**
30-day death, n (%)				
ProFS	**0 (0.0)**	**0 (0.0)**	**5 (21.7)**	**18 (78.3)**
SEED	**0 (0.0)**	**3 (12.5)**	**6 (25.0)**	**15 (62.5)**

ProFS study
Time course of presepsin by survival status



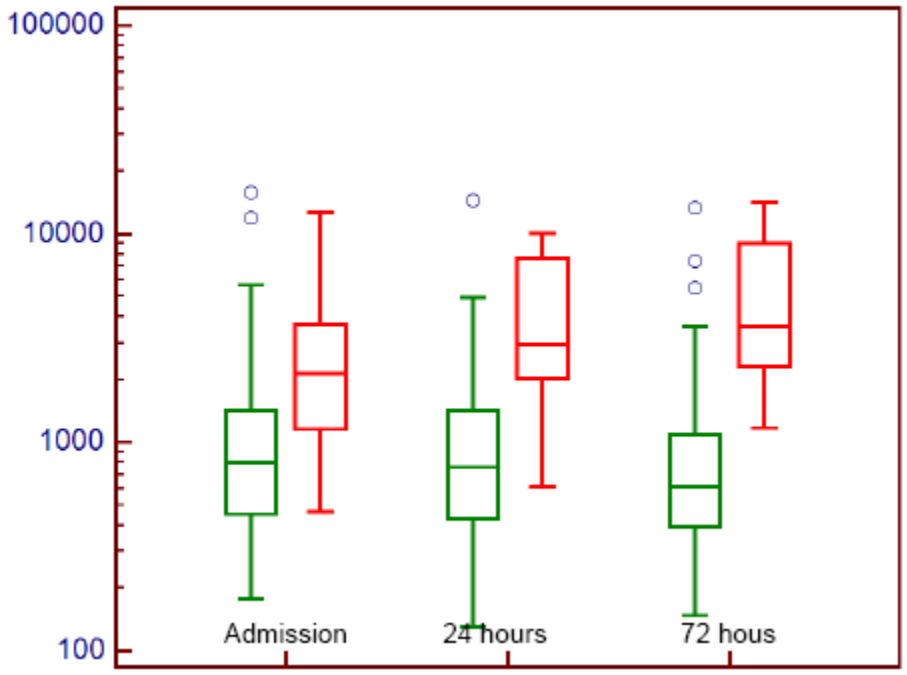
SEED study
Time course of presepsin by combined endpoint status

blue line: favourable outcome, n=77; red line: worse outcome (combined endpoint), n=37

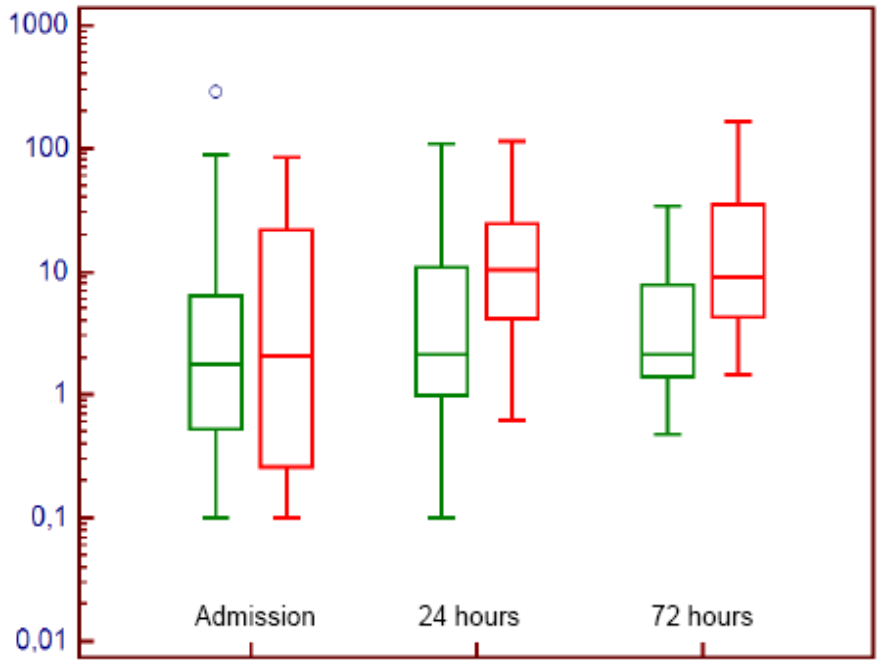


ProFS study
Time course of presepsin and PCT by survival status

Presepsin



PCT



Green: survivors; Red: non-survivors

Medical need of a biomarker for sepsis

James Faix, MD, Stanford University: Biomarkers of sepsis. Crit Rev Lab Sci 2013;50:23-26

1. Capability of detecting patients with elevated risk or developing severe sepsis

- **Presepsin provided reliable discrimination between controls, SIRS and sepsis as well as between sepsis, severe sepsis and septic shock.**

2. Capability of identifying septic patients who need more careful monitoring

- **Presepsin allowed prognosis and early prediction of 30-day mortality and combined endpoint already at admission.**

3. Capability of monitoring therapeutic measures

- **Presepsin values showed close association to the course of the disease.**

Conclusion

Presepsin demonstrated a strong relationship with disease severity and outcome. Presepsin provided reliable discrimination between SIRS and sepsis as well as prognosis and early prediction of 30-day mortality and combined endpoint already at admission. Moreover, presepsin values showed close association to the course of the disease.

The PATHFAST system allows the quantitative determination of presepsin also in whole blood samples and **may improve the management of patients presenting with early sepsis in the emergency room.**

Contemporary biochemical sepsis markers

The role of contemporary biochemical sepsis markers

- Interleukin 6 (IL-6)
- C-reactive protein (CRP)
- Procalcitonin (PCT)

remains controversely discussed!

James Faix, MD, Stanford University: Biomarkers of sepsis. Crit Rev Lab Sci 2013;50:23-26

Contemporary biochemical sepsis marker: Procalcitoinin

- PCT's predictive power appears to be significant ***only later*** in the course of illness

- PCT levels vary early in infection. Elevated levels on admission to an intensive care unit probably **are not helpful.**

- Recently, the results of randomized trials testing whether knowledge of PCT levels resulted in more effective recognition and treatment of severe sepsis,

did not support its use.

James Faix, MD, Stanford University: Biomarkers of sepsis. Crit Rev Lab Sci 2013;50:23-26

Definition of sepsis

1992: ACCP-SCCM Consensus Conference: definitions for sepsis and organ failure *(Crit Care Med 1992;20:864-874)*:

Systemic reponse to infection: *manifested by two or more criteria of the systemic inflammatory response syndrome (SIRS) as a result of infection.*

Update 2003: SCCM/ESICM/ATS/SIS International Sepsis Definitions Conference *(Crit Care Med 2003;31:1250-1256)*:

Strongly suspected infection *associated with two or more fulfilled criteria of the systemic inflammatory response syndrome (SIRS).*

- **ACCP**: American College of Chest Physicians
- **SCCM**: Society of Critical Care Medicine
- **ESICM**: European Society of Intensive Care Medicine
- **ATS**: American Thoratic Society
- **SIS**: Surgical Infection Society

Procedure of diagnosing sepsis according to 2003 updated guidelines

1. Recognition of bacterial infection by clinical signs followed by microbial confirmation (blood culture)
2. Examination of the SIRS criteria in order to assess systemic infection.

Consequences:

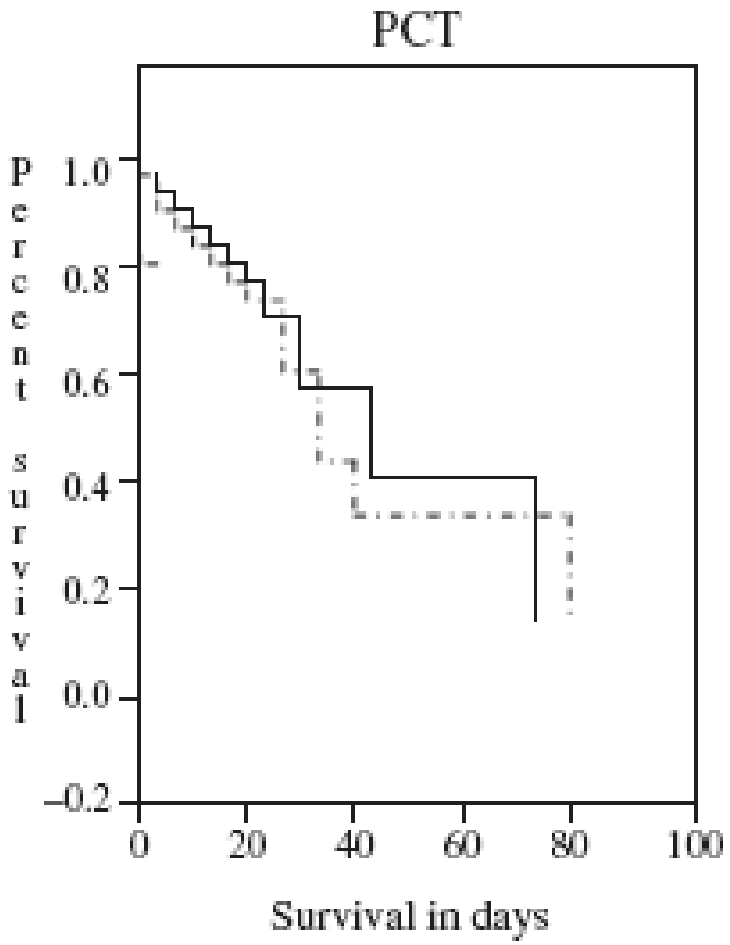
The diagnosis of sepsis according to the updated guidelines

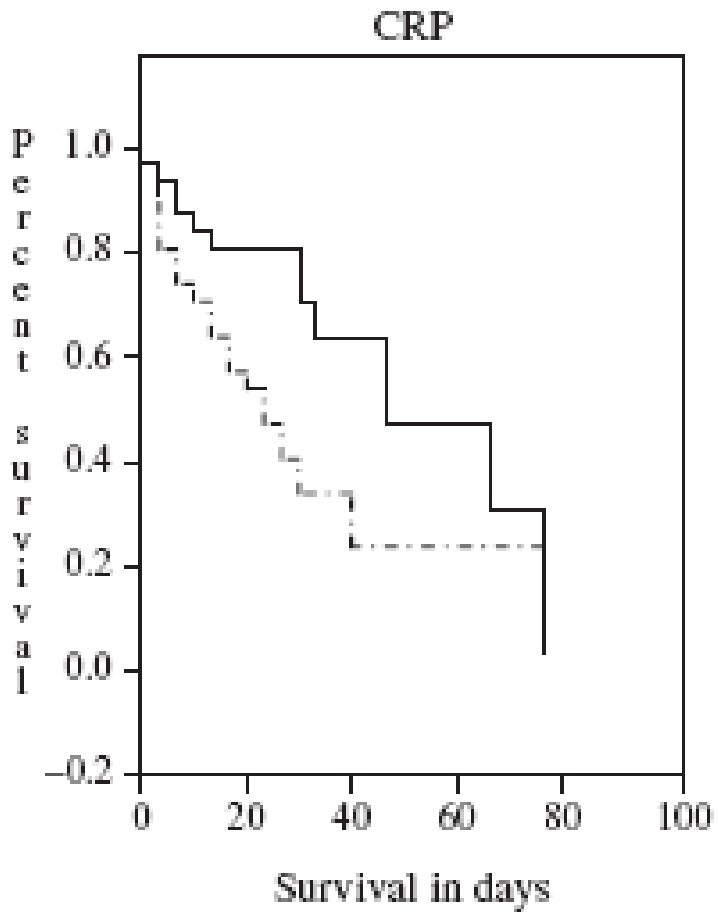
"SIRS plus evidence or suspicion of infection"

includes many patients who are unlikely to experience significant morbidity or mortality.

The mortality risk of severe sepsis or sepstic shock (>30%) exceeds that of sepsis (<10%) significantly.

Ruiz-Alvarez M, et al. Diagnostic efficay and prognostic value of serum PCT. J intensive Care Med 2009;24:63-72





Procalcitonin was not related to mortality (p=0.48)

Objective

To examine:

- whether presepsin meets the medical need of a biomarker for sepsis

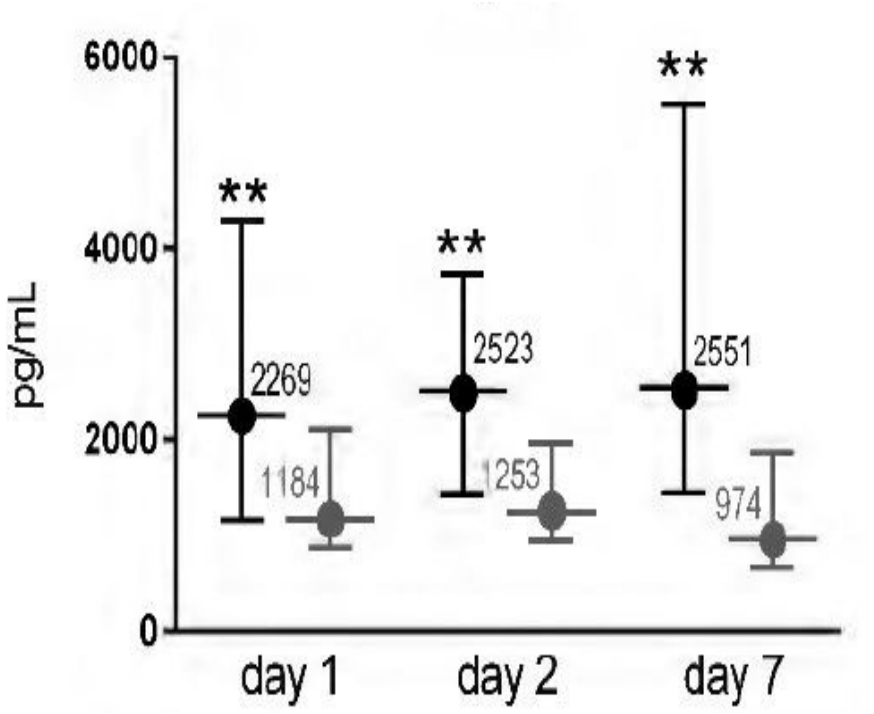
- the diagnostic and prognostic validity of presepsin in patients suspicious of sepsis admitted to an emergency department (ED)

ProFS study
Biochemical markers and clinical scores

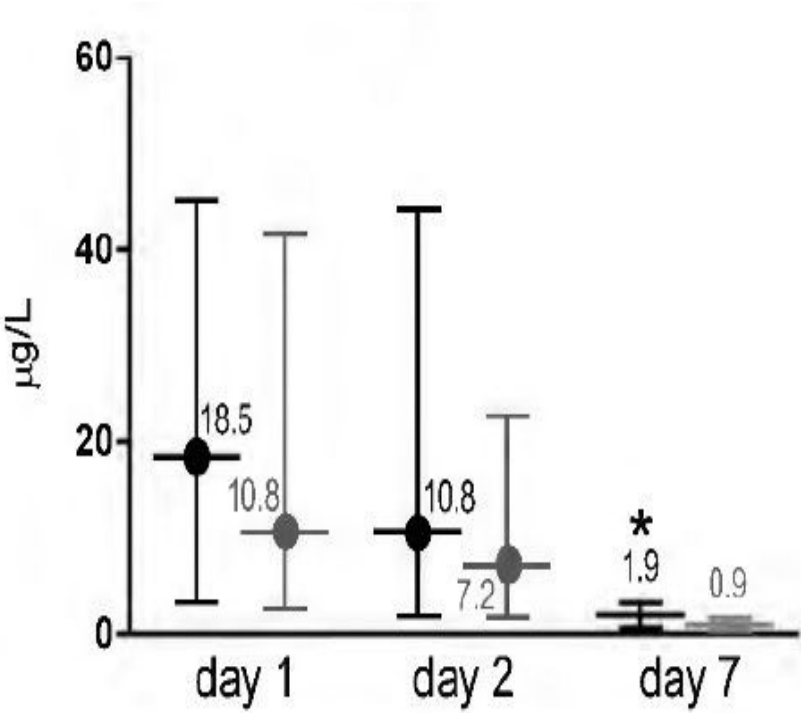
	Uncomplicated sepsis (N=85)		Severe sepsis or septic shock (N=55)		
	Median	95% CI	Median	95% CI	P-value*
IL-6, pg/ml	125	80 - 213	265	113 - 790	0.0123
CRP, mg/dl	148.3	93.7 - 190.4	195.7	125.1 - 260.8	0.0315
PCT, ng/ml	**1.44**	0.66 - 2.24	**3.05**	1.74 - 8.47	0.0065
Presepsin, pg/ml	**782**	559 - 932	**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

ALBIOS trial:
Time course of presepsin and PCT during ICU stay by survival status

Presepsin



Procalcitonin



Masson S, et al. Presepsin (soluble CD14 subtype, sCD14-ST) and procalcitonin for mortality prediction in sepsis. Data from the Albumin Italian Outcom Sepsis Trian (ALBIOS) trial. Crit Care 2014;18:R6

Review Article

Presepsin as a novel sepsis biomarker

Qi Zou, Wei Wen, Xin-chao Zhang

Emergency Medicine Department, Beijing Hospital, Beijing 100730, China

World J Emerg Med **2014**;5(1):16-19

DATA SOURCES: A literature search using multiple databases was performed for articles, especially meta-analyses, systematic reviews, and randomized controlled trials.

RESULTS: Compared with other markers, presepsin seems to have a better sensitivity and specificity in the diagnosis of sepsis. Presepsin as a biom1arker is not only suitable for the early diagnosis of sepsis, but also for the assessment of its severity and prognosis.

CONCLUSIONS: Presepsin has a higher sensitivity and specificity in the diagnosis of sepsis as a new biomarker, and is a predictor for the prognosis of sepsis. More importantly, preseptin seems to play a crucial role as a supplemental method in the early diagnosis of sepsis. Since there is no multicenter study on the relationship between presepsin and sepsis, further studies on the clinical values of presepsin are needed.