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Biochemical background

mCD14 – sCD14 – sCD14-ST *(= Presepsin)*

- Glycoprotein membrane anchored receptor of monocytes/macrophages **(mCD14).**
- Captures with toll-like receptor 4 (TLR4) circulating lipopolysaccharide (LPS) and LPS binding protein (LPBP) and activates the TLR4-specific proinflammatory signaling cascade against infectious agents.
- Simultaneously the LPS-LPBP-CD14 complex is released into circulation by shedding of CD14 from the cell, forming soluble CD14 **(sCD14).**

➢ ***mCD14 regulates early proinflammatory LPS response.***

➢ ***sCD14 plasma concentrations are elevated in sepsis.***

- Plasma protease activity generates another molecule fragment named soluble CD14 subtype (**sCD14-ST or Presepsin**).

➢ ***First clinical studies revealed superior results compared to sCD14.***

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Presepsin plasma concentration (pg/ml) in healthy controls (N=119) and in patients with sepsis (N=140)

	Controls	Patients with sepsis
Lowest value	60	338
Highest value	365	15757
Mean (95% CI)	159 (148 – 171)	2563 (1458 – 3669)
Standard deviation	62	3456
5th percentile	92	356
95th percentile	320	12149
Upper reference limit (URL	**320*)**	

***) No influence of age or gender**

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Evaluation of the diagnostic validity in comparison to established diagnostic tools

- **Inclusion:** 140 patients admitted to the **Emergency Room** with SIRS and suspected severe infection.
- **Biomarkers**
- **Clinical scores:** APACHE II, MEDS, GCS, SOFA
- **Endpoints:** 30–day mortality, ICU, dialysis, mechanical ventilation

Study population:

Sepsis grade	Survivors	Non-survivors
Low grade sepsis (N=85)	82	3 ***(4%)***
Severe sepsis (N=40)	30	10 ***(25%)***
Septic shock (N=15)	5	10 ***(67%)***

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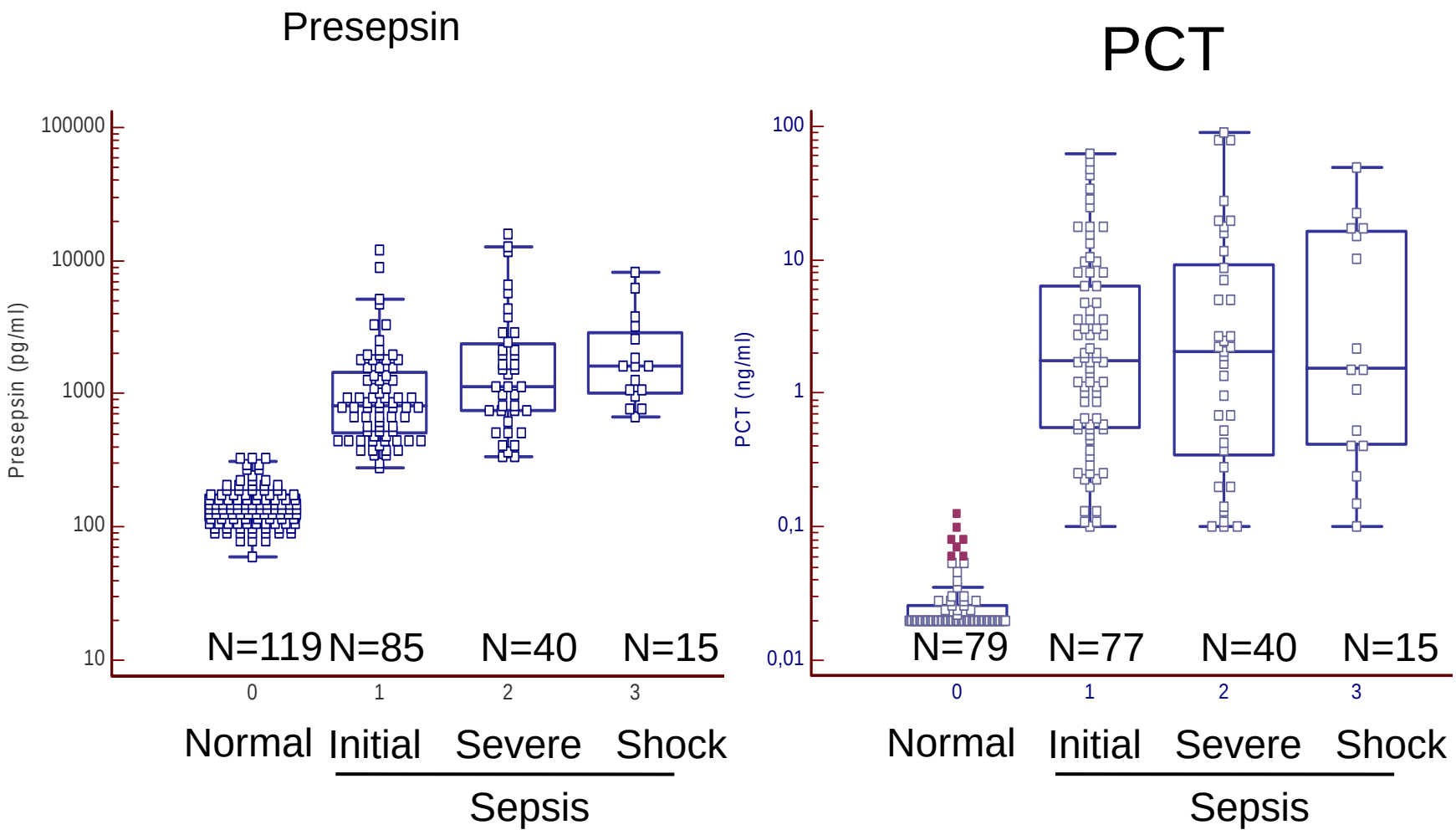
Presepsin increases with severity of sepsis



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Presepsin discriminates between disease severity and outcome

Marker	Low grade/severe sepsis p – value*	Survival/non-survival p – value*
IL-6	0.0123	0.0584
CRP	0.0315	0.3824
PCT	0.0065	0.7452
Presepsin	< 0.0001	< 0.0001
APACHE II	< 0.0001	< 0.0001
MEDS	< 0.0001	< 0.0001
SOFA	0.0005	0.0007

*) Significant discrimination if p<0.05

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Relationship of prespsin plasma concentration with mortality

(in comparison to procalcitonin)

Presepsin (pg/ml)	**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	**36**	**32**	**29**	**20**
Non-survivors	**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**

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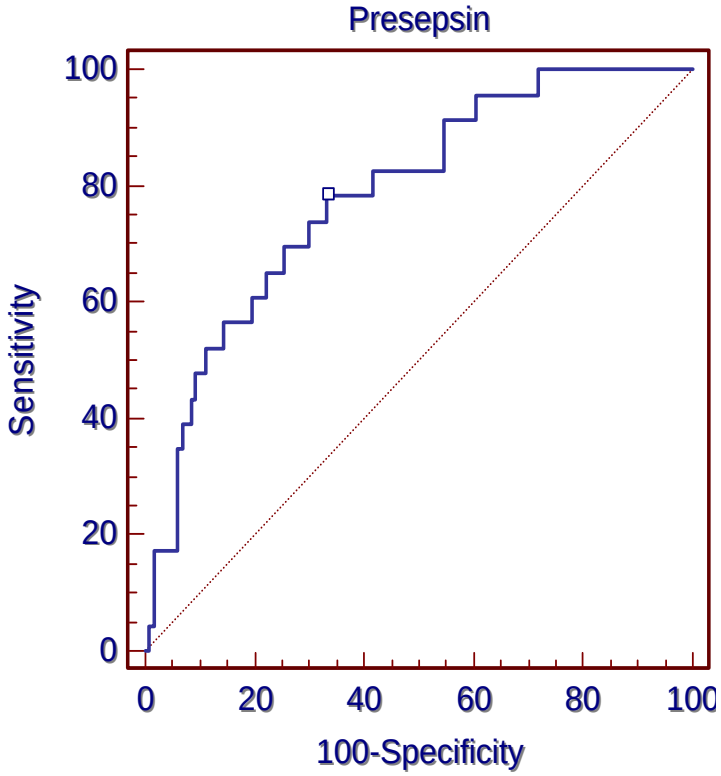
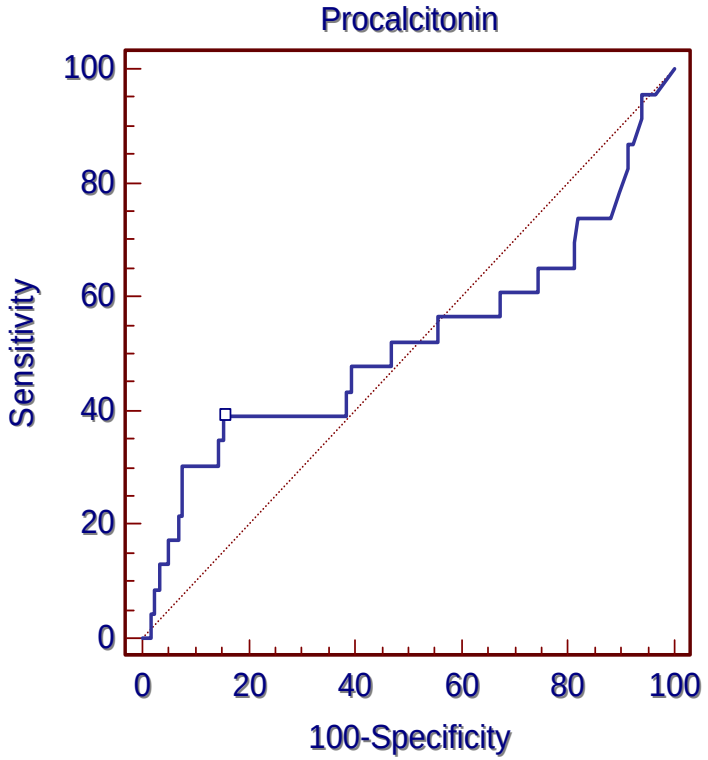
Risk of mortality prediction

ROC curves based on plasma concentration at admission

(Survivors N=117; Non-survivors N=23)





AUC = 0.797
Sens=78.3%
Spec=66.7
Cutoff=1108 pg/ml

< P < 0.0001 >

AUC = 0.519
Sens=39.1%
Spec=84.6%
Cutoff=13.43 ng/ml

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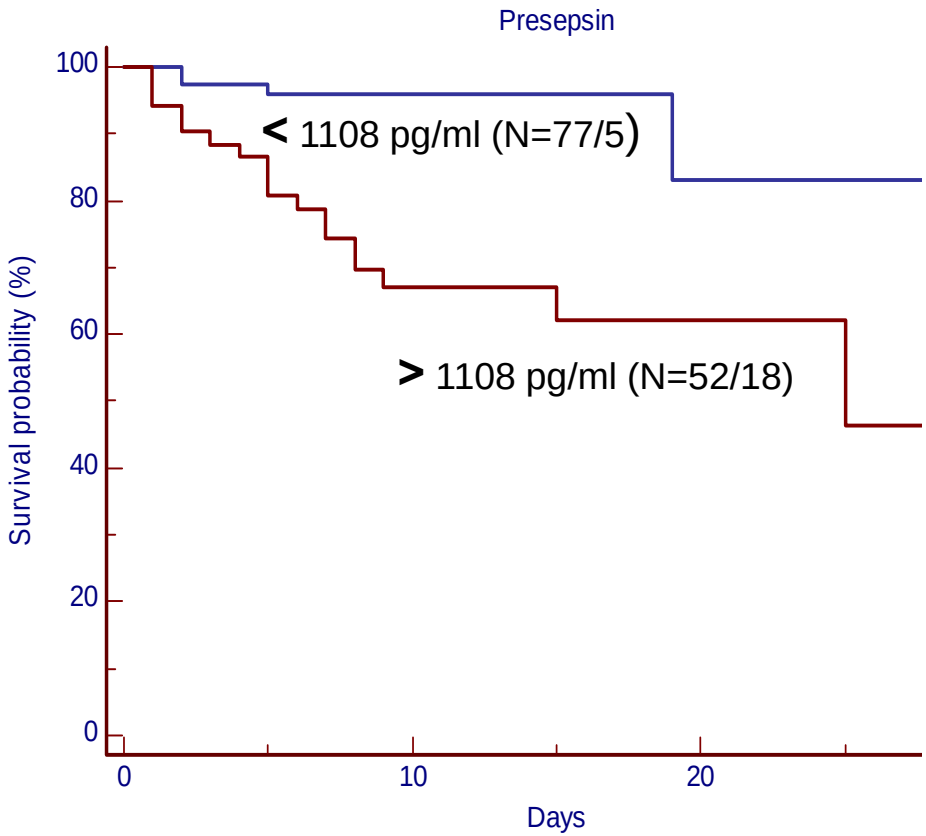
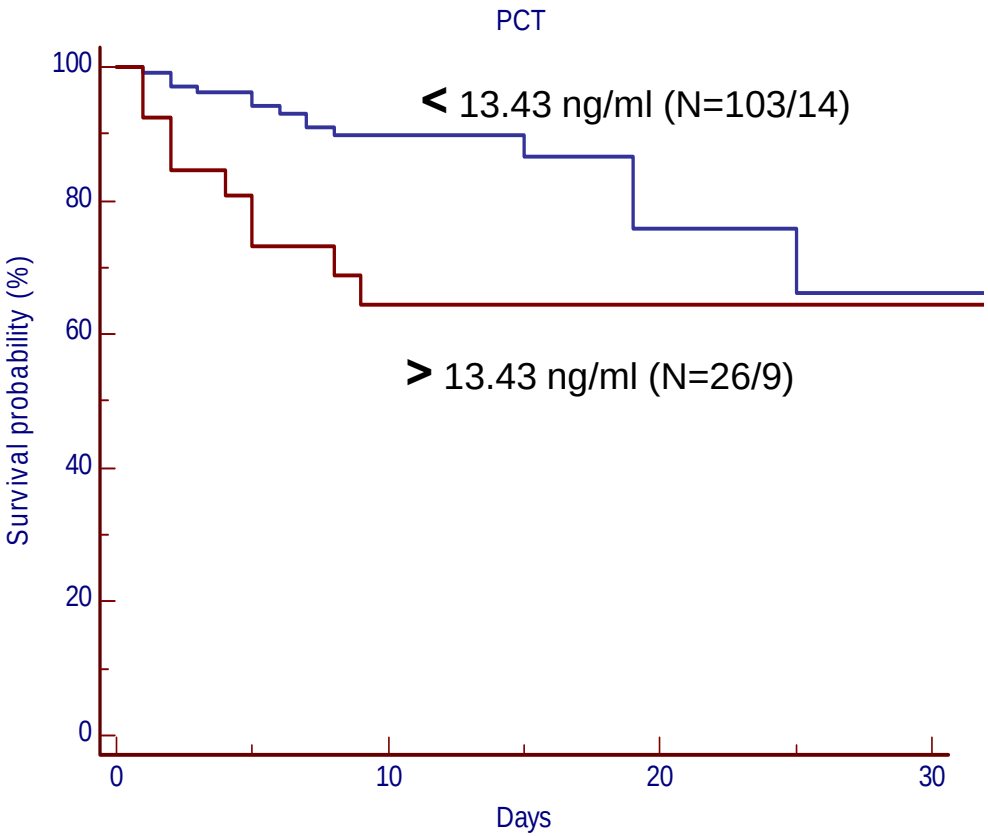
Kaplan-Meier curves for risk of 30 day mortality prediction at admission



Chi-square =17.56
P < 0.0001
HR: 0.16 95%CI: 0.068 – 0.038



Chi-square=5,64
P = 0,0175
HR=0,38 95% CI 0,1-0,8

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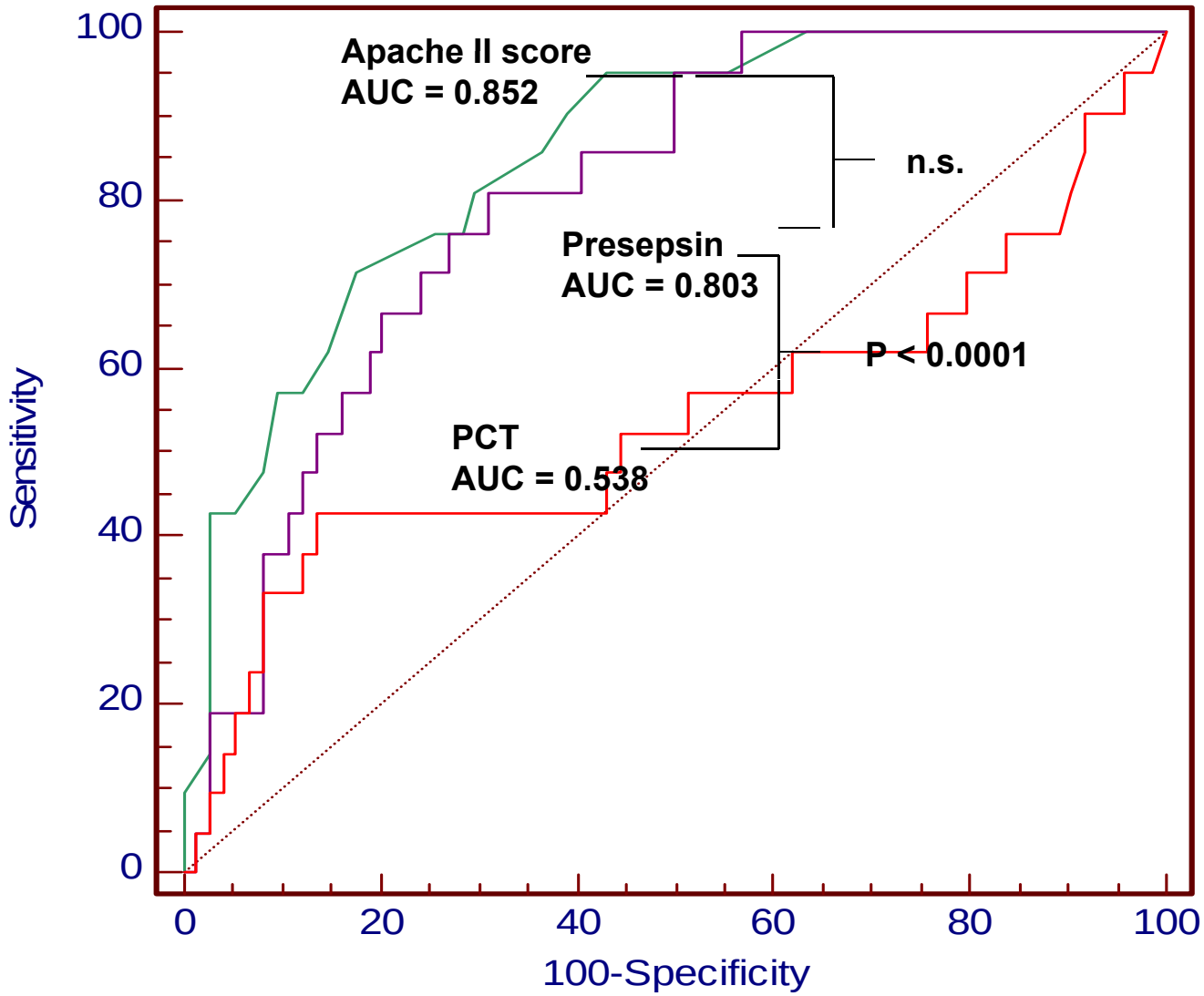
Risk of mortality prediction

ROC curves of baseline APACHE II score, PCT, and presepsin in patients with severe sepsis and septic shock



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Combining clinical scores and presepsin improves risk of mortality prediction

	C-statistic		Net Reclassificatiom
Score	**AUC alone**	**AUC with Presepsin**	**NRI**
APACHE II	0.815	**0.905**	21.05 + 33.34 = 54.39%
GCS	0.763	**0.931**	03.58 + 73.33 = 76.91%
MEDS	0.819	**0.936**	**22.67 + 40.00 = 62.67%**
SOFA	0.747	**0.917**	22.45 + 33.33 = 55.78%

MEDS score and Prespsin

~23% of alive patients more are re-classified in the right direction (down) and 40% of dead patients more are re-classified in the right direction (up)

NRI = 0.63

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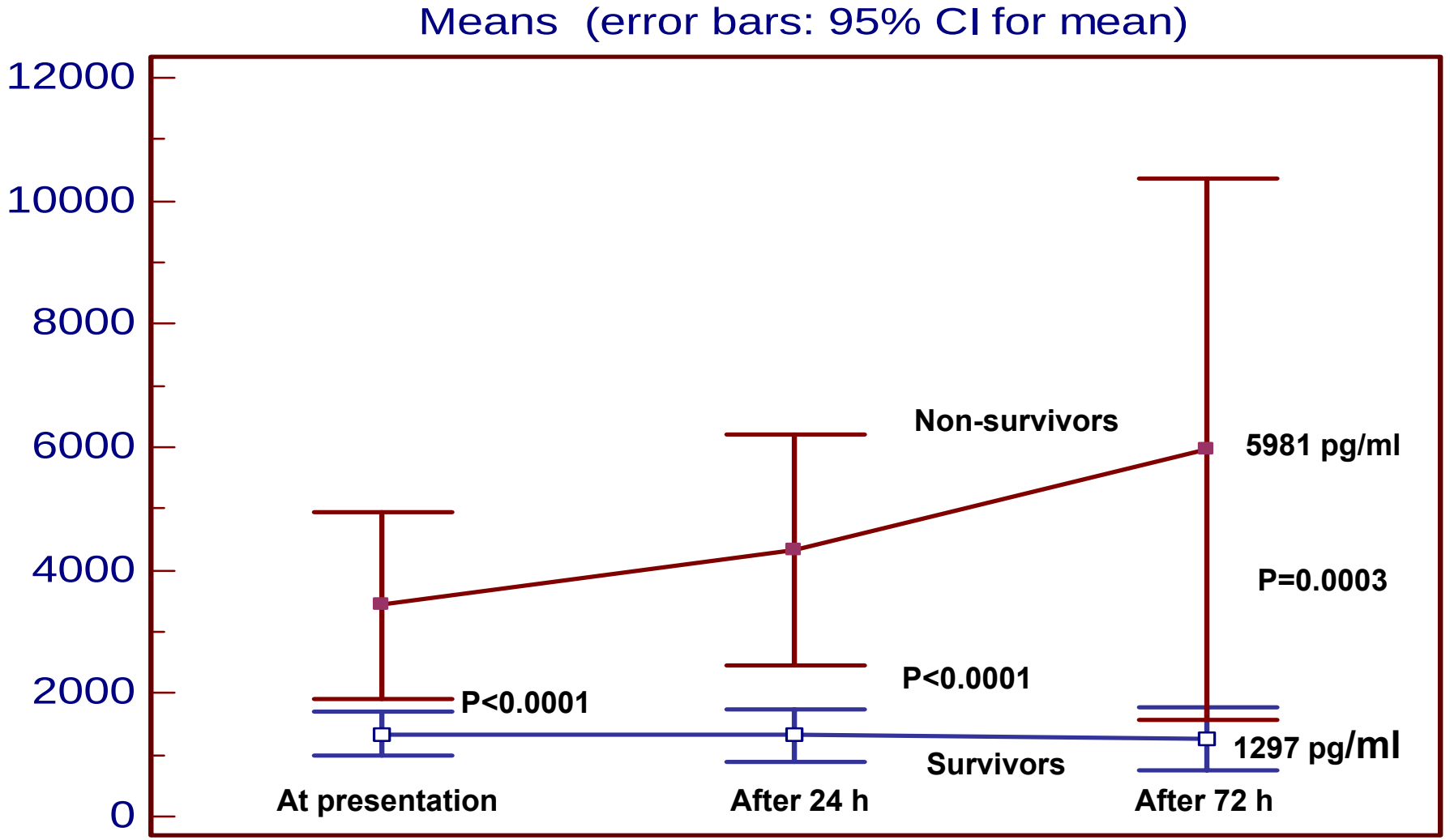
Disease monitoring

Presepsin levels at baseline, after 24 h, and after 72 h



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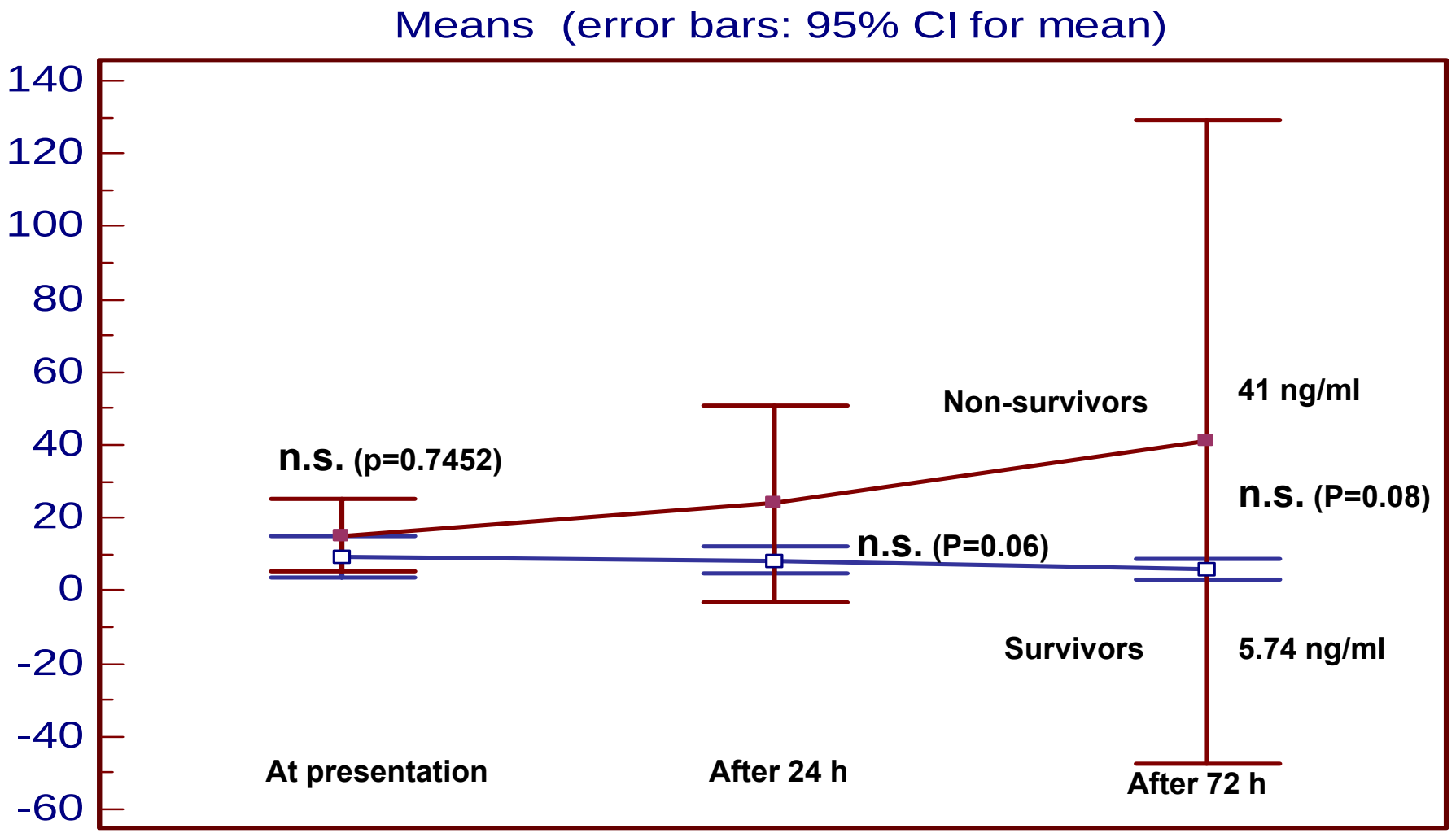
PCT levels at baseline, after 24 h, and after 72 h



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Preliminary Decision Cutoffs

Presepsin (pg/ml)	Diagnosis	Clinical consequenses based on study data
< 200	Exclusion of sepsis	No blood culture necessary
≥ 300	Systemic infection (sepsis) possible	Further diagnostic measures including blood culture
≥ 500	Moderate risk of progression of systemic infection (severe sepsis)	Early goal directed therapy after taking blood cultures
≥ 1000	High risk of progression of systemic infection (severe sepsis/septic shock). **High risk for 30 day mortality comparable to APACHE score ≥ 25**	Consideration of adjunctive therapy, e.g. rhAPC

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Comparison of PCT and Presepsin

Indication/Discrimination	PCT	Presepsin
Healthy subjects vs. septic patients	+ + +	+ +
SIRS vs. sepsis	+ +	+ +
Differentiation of sepsis severity	-	+
Correlation with clinical scores	+	+ +
Mortality Prognosis	+	+ + +
Monitoring (course of the disease)	+	+ +
Sum	8	12

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Summary

- sCD14-ST (Presepsin) is a circulating molecule fragment derived from sCD14 and serves as mediator of LBS effects.
- Presepsin differs between healthy individuals and septic patients.
- Presepsin concentrations are elevated in patients with sepsis depending on outcome and disease severity.
- Presepsin could be useful in
  - Diagnosis of sepsis
  - Early risk prediction of mortality at admission
  - Assessment of the disease severity and monitoring