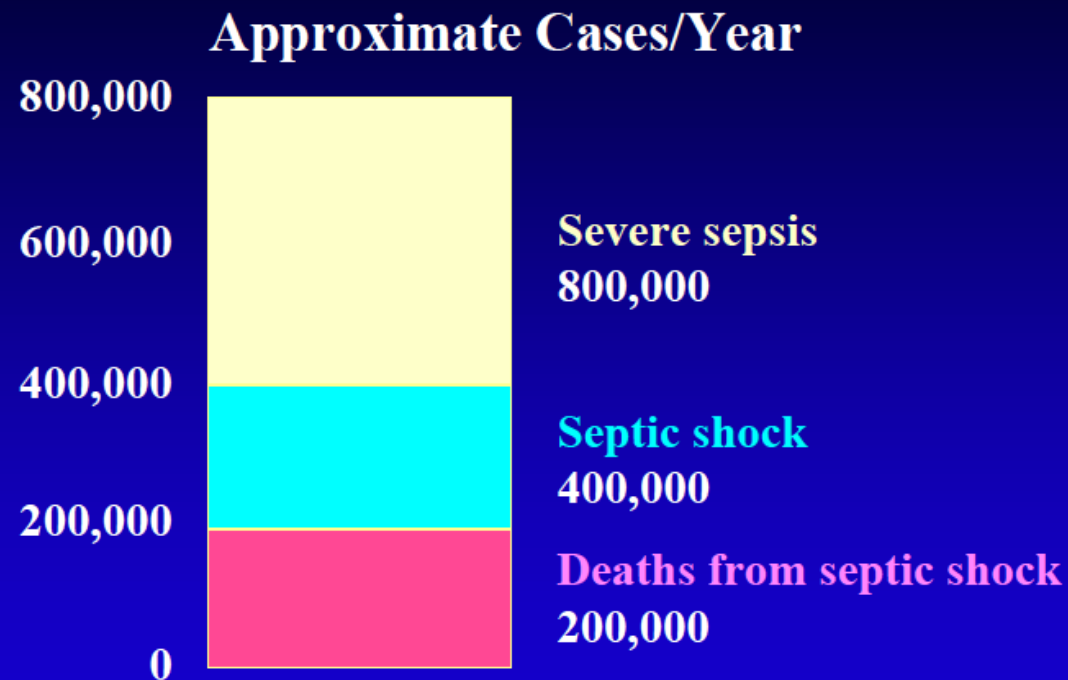# Presepsin: diagnostic and prognostic utility in ICU treatment

PD Dr. med. Ursula Hoffmann

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Faculty of Medicine Mannheim, University of Heidelberg, Germany**

2nd International Presepsin Workshop, 21.9.2014, Munich

Biochemical marker used in sepsis diagnostics

- **CRP** (C reactive protein)
- **IL-6** (Interleukine 6)
- **PCT** (Procalcitonin)
- **LBP** (lipopolysacharide binding protein)
- **Presepsin (sCD14ST)**

Clinical use of Presepsin

» Rapid diagnosis and prognosis of sepsis

» High prognostic value at presentation

» For emergency and intensive care use

CRITICAL CARE

RESEARCH   **Open Access**

Diagnostic and prognostic utility of soluble CD 14 subtype (presepsin) for severe sepsis and septic shock during the first week of intensive care treatment

Michael Behnes[1], Thomas Bertsch[2], Dominic Lepiorz[1], Siegfried Lang[1], Frederik Trinkmann[1], Martina Brueckmann[3], Martin Borggrefe[1] and Ursula Hoffmann[1*]

2nd International Presepsin Workshop, 21.9.2014, Munich

Design – Mannheim Sepsis Study (MaSep)

- Consecutive enrollment of 116 patients presenting to the internal intensive care unit (ICU) with proven criteria of SIRS (systemic inflammatory-response syndrome), sepsis, severe sepsis and septic shock were evaluated according to the criteria of the ACCP/SCCM consensus statement .

- Blood samples for measurement of presepsin were collected on day 1, 3 and 8 after the clinical onset of sepsis.

- Presepsin was measured by the PATHFAST® immunoassay analytical system (PROGEN Biotechnik GmbH, Germany; Mitsubishi chemical medience corporation, Japan).

- Clinical follow up to 30 days, prognostic endpoint 30-day and 6 month all-cause-mortality.

- Mannheim Sepsis Study (MaSep), ClinicalTrials.gov Identifier: NCT01535534.

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Table 1 Baseline characteristics of the Mannheim Sepsis Study (MaSep)

	Controls (n=60)	SIRS (n=9)	Sepsis (n=5)	Severe Sepsis (n=28)	Septic Shock (n=74)
Age, years (mean, range)	62 (42-87)	74 (61-81)	66 (50-81)	66 (26-87)	68 (26-88)
Gender, n (%)					
Male	29 (48)	5 (56)	4 (80)	21 (75)	52 (70)
Female	31 (52)	4 (44)	1 (20)	7 (25)	22 (30)
Site of infection, n (%)					
Lung	-	-	5 (100)	20 (71)	41 (55)
Urinary tract	-	-	-	3 (11)	4 (5)
Abdominal	-	-	-	3 (11)	12 (16)
Central nervous system	-	-	-	-	-
Skin	-	-	-	1 (4)	3 (4)
Heart	-	-	-	-	-
Neutropenia	-	-	-	-	-
Blood	-	-	-	1 (4)	7 (9)
Others	-	-	-	-	7 (8)
Laboratory values, mean ± SEM					
White blood cells (10^9/L)	-	14.5 ± 1.7	19.2 ± 3.1	17.4 ± 3.1	19.5 ± 1.8
Platelets, (10E9/L)	-	210 ± 216	305 ± 202	218 ± 214	191 ±142
Bilirubin, mg/dl	-	0.8 ± 0.2	0.5 ± 0.1	1.1 ± 0.3	2.9 ± 0.7
Creatinine, mg/dl	-	1.1 ± 0.1	1.2 ± 0.2	2.4 ± 0.3	2.7 ± 0.2
C reactive proteine, mg/l	-	68 ±16	155 ± 28	178 ± 24	197 ± 12
Procalcitonin, ng/ml	-	2.0 ± 0.9	4.3 ± 2.8	6.9 ± 2.0	22.2 ± 4
Interleukin 6, pg/ml	-	335 ± 154	142 ± 53	1385 ± 829	21089 ± 15437
pCO_2 (mmHg)	-	43 ± 5	49 ± 14	45 ± 4	44 ± 2
Positive blood cultures, n (%)	-	0 (0)	0 (0)	8 (29)	25 (34)
ICU parameters, mean ± SEM					
ICU days	-	10 ± 2	8 ± 2	10 ± 2	15 ± 2
Ventilation days	-	3 ± 1	4 ± 2	6 ± 2	9 ± 2
Catecholamine days	-	2 ± 1	0 ± 0	2 ± 1	7 ± 1
Renal replacement therapy days	-	0 ± 0	0 ± 0	1 ± 0.6	3 ± 1
APACHE II, mean ± SEM	-	24 ± 2	18 ± 3	20 ± 2	27 ± 1
SOFA score, mean ± SEM	-	7.6 ± 1.1	6.2 ± 1.8	6.1 ± 0.5	11.8 ± 0.4
All-cause mortality					
30 days					
Death	0 (0)	5 (56)	2 (40)	10 (36)	42 (57)
Survivor	60 (100)	4 (44)	3 (60)	18 (64)	32 (43)
6 months					
Death	0 (0)	5 (56)	3 (60)	12 (43)	53 (72)
Survivor	60 (100)	4 (44)	2 (40)	16 (57)	21 (28)

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Table 2 Univariate correlations of PRESEPSIN with laboratory and clinical parameters in all patients (n=116) at day 1

	r	p value
Creatinine	0.28	0.002
Bilirubin	0.20	0.04
White blood cells	0.17	0.07
Platelets	0.09	0.4
C reactive proteine (CRP)	0.22	0.02
Procalcitonin (PCT)	0.36	0.0001
Interleukin 6	0.39	0.0001
pCO2	-0.25	0.007
Systolic blood pressure	-0.19	0.04
Intensive care days	0.22	0.02
Mechanical ventilation days	0.19	0.04
Renal replacement days	0.36	0.0001
Catecholamines days	0.21	0.03
SOFA score	0.23	0.02
APACHE II score	0.28	0.004
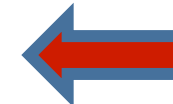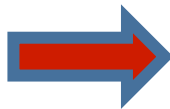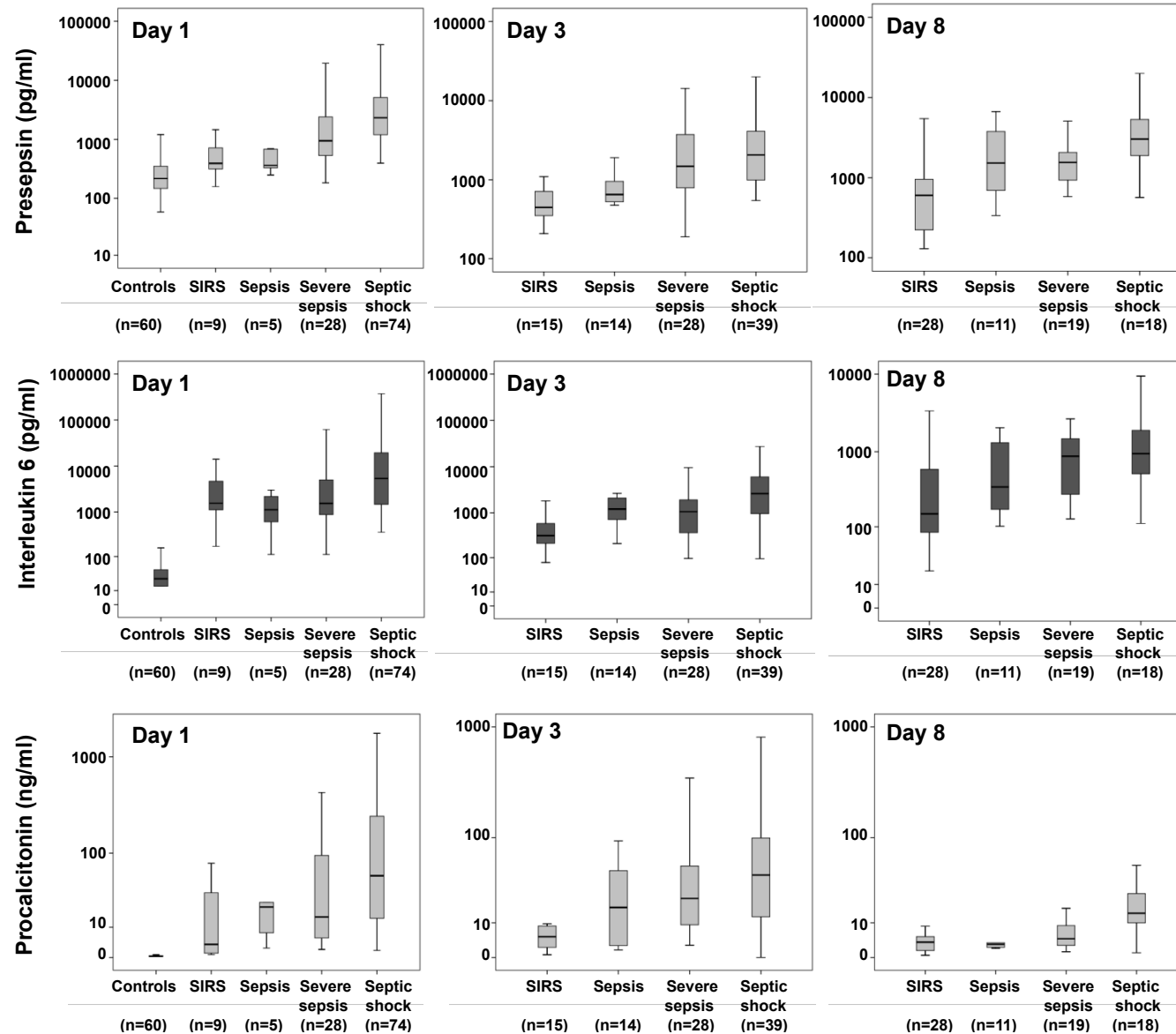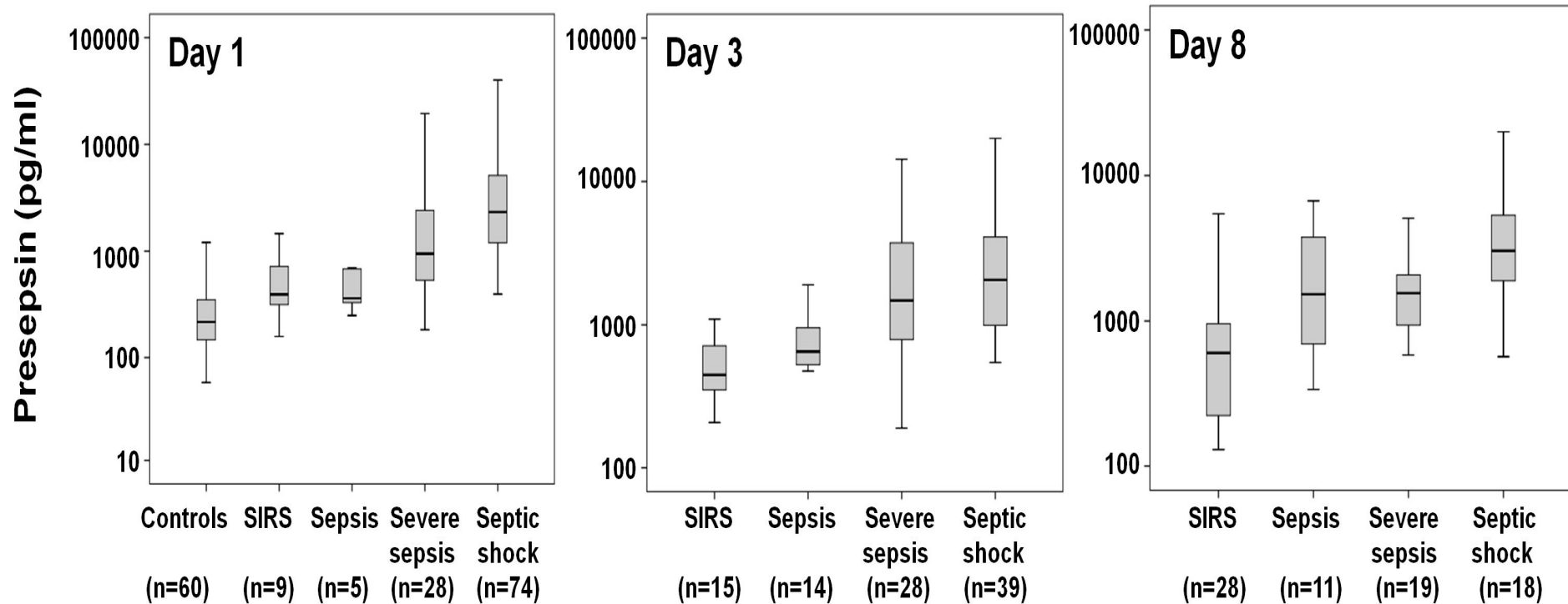
Presepsin-levels in patients admitted to the internal ICU with SIRS, Sepsis, Severe Sepsis and Septic Shock on day 1, 3 and 8. 60 healthy individual served as a control group at day 1.
Data are presented as medians with 25th and 75th percentiles (boxes) and 5th and 95th percentiles (whiskers).

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Table 3 Diagnostic performance of biomarkers for diagnosis of severe sepsis and septic shock at days 1, 3 and 8 of ICU treatment, analyzed as area under the curves, AUCs (95% CI)

	Presepsin	Interleukin-6	Procalcitonin	CRP	White blood cells
Day 1					
Septic shock (n=74)	0.80 (0.73-0.86) *p=0.0001*	0.86 (0.80-0.91) *p=0.0001*	0.83 (0.77-0.90) *p=0.0001*	0.62 (0.49-0.74) p=0.06	0.53 (0.41-0.62) p=0.7

Day 1: Controls n=60; SIRS n=9; sepsis n=5; severe sepsis n=28; septic shock n=74.

	Presepsin	Interleukin-6	Procalcitonin	CRP	White blood cells
Day 3					
≥Sepsis (n=81)	0.84 (0.72-0.96) *p=0.0001*	0.81 (0.70-0.92) *p=0.001*	0.69 (0.52-0.87) *p=0.03*	0.69 (0.54-0.83) *p=0.04*	0.73 (0.60-0.87) *p=0.009*
≥Severe sepsis (n=67)	0.80 (0.70-0.91) *p=0.0001*	0.71 (0.60-0.81) *p=0.003*	0.66 (0.52-0.80) *p=0.02*	0.61 (0.49-0.74) p=0.1	0.59 (0.47-0.72) p=0.2
Septic shock (n=39)	0.72 (0.61-0.82) *p=0.0001*	0.76 (0.66-0.87) *p=0.0001*	0.66 (0.55-0.77) *p=0.01*	0.72 (0.62-0.83) *P=0.0001*	0.57 (0.45-0.70) p=0.3

Day 3: SIRS n=15; sepsis n=14; severe sepsis n=28; septic shock n=39.

	Presepsin	Interleukin-6	Procalcitonin	CRP	White blood cells
Day 8					
≥Sepsis (n=48)	0.82 (0.71-0.93) *p=0.0001*	0.74 (0.61-0.87) *p=0.001*	0.64 (0.50-0.78) p=0.06	0.69 (0.54-0.84) *p=0.01*	0.75 (0.64-0.87) *p=0.001*
≥Severe sepsis (n=37)	0.77 (0.65-0.88) *p=0.0001*	0.73 (0.61-0.85) *p=0.001*	0.68 (0.55-0.81) *p=0.01*	0.65 (0.51-0.78) *p=0.04*	0.71 (0.58-0.83) *p=0.004*
Septic shock (n=18)	0.79 (0.66-0.92) *p=0.0001*	0.69 (0.55-0.83) *p=0.02*	0.78 (0.65-0.92) *p=0.001*	0.67 (0.53-0.81) *p=0.04*	0.68 (0.53-0.84) *p=0.02*

Day 8: SIRS n=28; sepsis n=11; severe sepsis n=19; septic shock n=18.

A minimal AUC was set at ≥0.75 (highlighted in bold type)

Table 4 Goodness criteria of presepsin for diagnosis of sepsis, severe sepsis and septic shock during the first week of ICU treatment

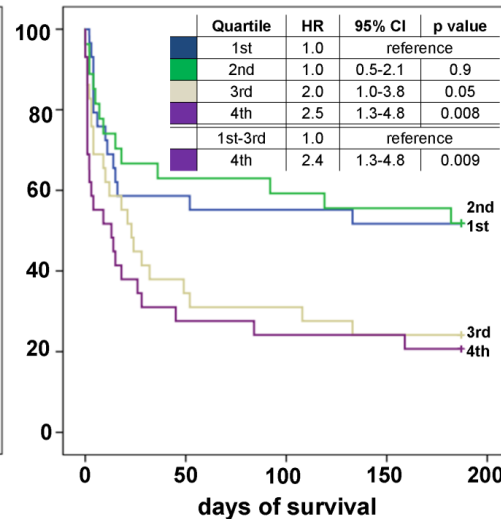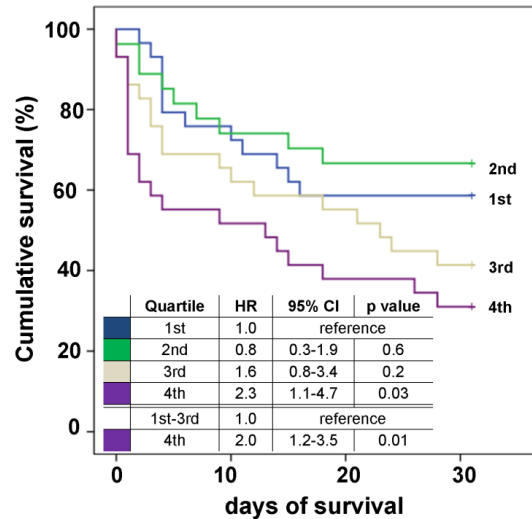|	AUC	cutoff (pg/ml)	accuracy (%)	sensitivity (%)	specificity (%)	PPV (%)	NPV (%)	relative risk	p value
Day 1									
≥Septic shock	0.80	700	82	91 (67/74)	77 (78/102)	74 (67/91)	92 (78/85)	8.9	0.0001
Day 3									
≥Sepsis	0.84	530	86	90 (73/81)	60 (09/15)	93 (73/79)	56 (09/16)	2.1	0.0001
≥Severe sepsis	0.80	600	80	91 (61/67)	54 (15/28)	82 (61/74)	71 (15/21)	2.9	0.0001
Day 8									
≥Sepsis	0.82	530	76	94 (45/48)	46 (13/28)	75 (45/60)	81 (13/16)	4.0	0.001
≥Severe sepsis	0.77	600	66	92 (34/37)	41 (16/39)	60 (34/57)	84 (16/19)	3.8	0.001
≥Septic shock	0.79	700	50	89 (16/18)	38 (22/58)	31 (16/52)	92 (22/24)	3.7	0.03

AUC: Area under curve; PPV and NPV: positive and negative predictive values.
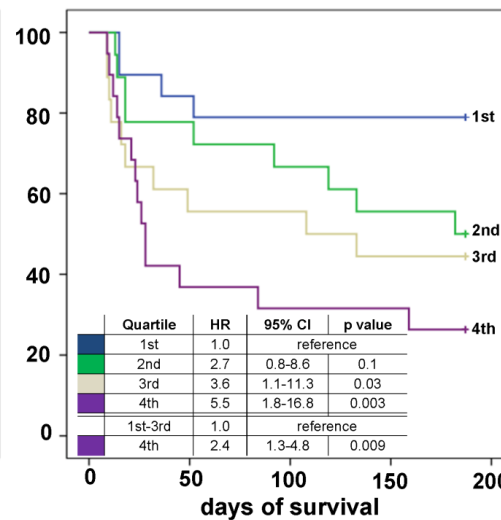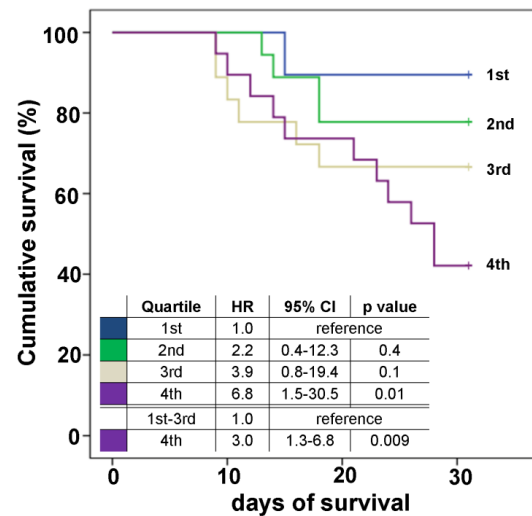Diagnostic goodness criteria have only been calculated when the diagnostic AUC was ≥0.75.

Table 5   Prognostic performance of biomarkers and ICU scores for 30 days and 6 months all-cause mortality during the 1st week of ICU treatment

	Presepsin	Interleukin-6	Procalcitonin	CRP	Leukocytes	SOFA	APACHE II
				AUC (95% CI) p value			
30 day all-cause mortality							
Day 1	0.64 (0.54-0.75) *p=0.008*	0.69 (0.55-0.76) *p=0.001*	0.59 (0.48-0.69) p=0.1	0.54 (0.43-0.65) p=0.5	0.51 (0.41-0.62) p=0.8	0.64 (0.52-0.77) *p=0.05*	0.70 (0.60-0.80) *p=0.0001*
Day 3	0.70 (0.59-0.81) *p=0.002*	0.69 (0.58-0.80) *p=0.002*	0.58 (0.46-0.70) p=0.2	0.64 (0.52-0.76) p=0.03	0.55 (0.42-0.67) p=0.5	0.65 (0.53-0.77) *p=0.04*	0.64 (0.51-0.77) *p=0.04*
Day 8	0.69 (0.56-0.82) *p=0.02*	0.67 (0.54-0.81) *p=0.03*	0.57 (0.41-0.73) p=0.4	0.61 (0.46-0.75) p=0.2	0.60 (0.46-0.75) p=0.2	0.69 (0.57-0.81) *p=0.007*	0.60 (0.42-0.78) p=0.3

58 of 116 patients died after 30 days corresponding to an all-cause mortality rate of 50%.
Significant p-values (p<0.05) are highlighted in bold type.

	Presepsin	Interleukin-6	Procalcitonin	CRP	Leukocytes	SOFA	APACHE II
6 months all-cause mortality							
Day 1	0.68 (0.58-0.78) *p=0.001*	0.66 (0.56-0.76) *p=0.05*	0.59 (0.49-0.70) p=0.1	0.57 (0.45-0.69) p=0.2	0.54 (0.43-0.65) p=0.5	0.67 (0.55-0.78) *p=0.01*	0.65 (0.54-0.76) *p=0.01*
Day 3	0.70 (0.59-0.80) *p=0.002*	0.70 (0.59-0.80) *p=0.001*	0.57 (0.45-0.69) p=0.3	0.61 (0.49-0.73) p=0.08	0.59 (0.47-0.71) p=0.2	0.64 (0.52-0.76) *p=0.04*	0.61 (0.48-0.74) p=0.1
Day 8	0.71 (0.58-0.83) *p=0.004*	0.67 (0.54-0.80) *p=0.02*	0.56 (0.42-0.70) p=0.4	0.63 (0.49-0.77) p=0.06	0.60 (0.46-0.74) p=0.2	0.71 (0.60-0.83) *p=0.001*	0.64 (0.44-0.84) p=0.2

72 of 116 patients died after 6 months corresponding to an all-cause mortality rate of 62%.
Significant p-values (p<0.05) are highlighted in bold type.

Day 1

Left plot (days of survival, 0–30):

Quartile	HR	95% CI	p value
1st	1.0	reference	
2nd	0.8	0.3-1.9	0.6
3rd	1.6	0.8-3.4	0.2
4th	2.3	1.1-4.7	0.03
1st-3rd	1.0	reference	
4th	2.0	1.2-3.5	0.01

Right plot (days of survival, 0–200):

Quartile	HR	95% CI	p value
1st	1.0	reference	
2nd	1.0	0.5-2.1	0.9
3rd	2.0	1.0-3.8	0.05
4th	2.5	1.3-4.8	0.008
1st-3rd	1.0	reference	
4th	2.4	1.3-4.8	0.009

Day 8

Left plot (days of survival, 0–30):

Quartile	HR	95% CI	p value
1st	1.0	reference	
2nd	2.2	0.4-12.3	0.4
3rd	3.9	0.8-19.4	0.1
4th	6.8	1.5-30.5	0.01
1st-3rd	1.0	reference	
4th	3.0	1.3-6.8	0.009

Right plot (days of survival, 0–200):

Quartile	HR	95% CI	p value
1st	1.0	reference	
2nd	2.7	0.8-8.6	0.1
3rd	3.6	1.1-11.3	0.03
4th	5.5	1.8-16.8	0.003
1st-3rd	1.0	reference	
4th	2.4	1.3-4.8	0.009

Kaplan-Meier survival curves evaluated
by quartiles of presepsin after 30 days
(left column) and 6 months (right column) of
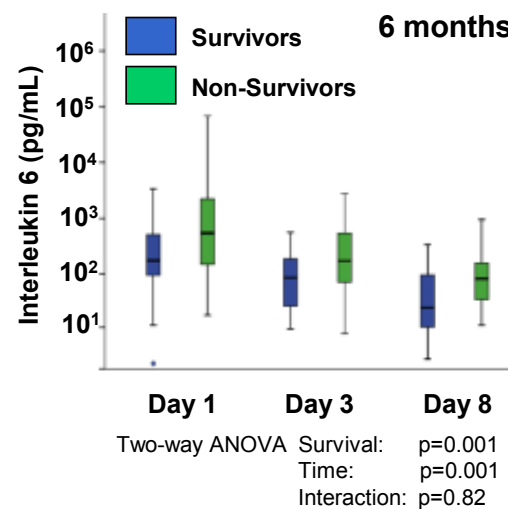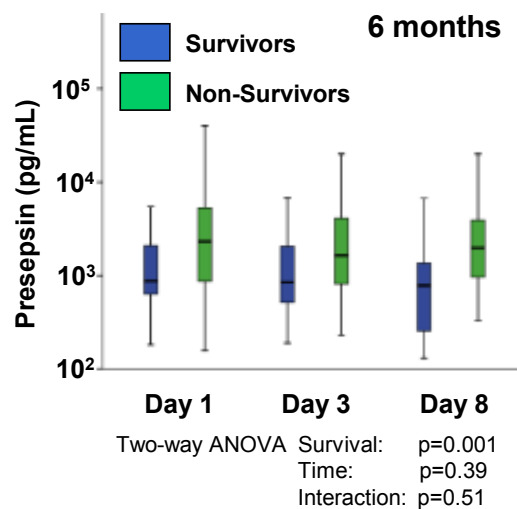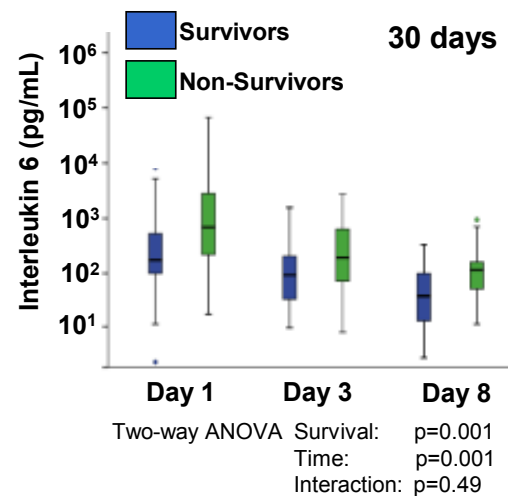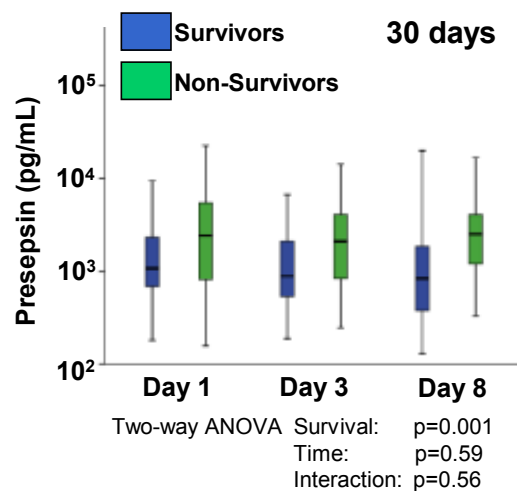follow up in the total study cohort
(n=116)

TABLE 6 Cox regression models to predict 30 days and 6 months all-cause mortality at days 1, 3 and 8 of intensive care treatment

	Model 1				Model 2			
	unadjusted				adjusted for age, sex, creatinine, ICU days, APACHE II			
Predictor	HR	95% CI	Chi-Square	p value	HR	95% CI	Chi-Square	p value
30 days all-cause mortality								
Day 1								
Log Presepsin (pg/ml)	1.9	1.2-3.0	6.9	0.009	2.2	1.2-4.1	42.9	0.02
Log Interleukin 6 (pg/ml)	1.7	1.4-2.2	20.5	0.0001	1.9	1.4-2.7	54.7	0.0001
Day 3								
Log Presepsin (pg/ml)	1.8	1.0-3.3	3.7	0.05	1.3	0.5-3.3	4.9	0.7
Log Interleukin 6 (pg/ml)	2.6	1.6-4.4	13.2	0.0001	3.2	2.0-5.4	28.3	0.0001
Day 8								
Log Presepsin (pg/ml)	2.5	1.3-5.0	7.4	0.007	7.5	2.4-23.3	22.6	0.001
Log Interleukin 6 (pg/ml)	3.9	1.6-9.4	9.2	0.003	6.0	1.9-19.2	18.3	0.002
6 months all-cause mortality								
Day 1								
Log Presepsin (pg/ml)	2.0	1.3-3.0	10.6	0.001	2.7	1.5-4.9	32.0	0.001
Log Interleukin 6 (pg/ml)	1.7	1.3-2.1	19.3	0.0001	1.7	1.3-2.3	36.5	0.0001
Day 3								
Log Presepsin (pg/ml)	1.9	1.2-3.2	6.5	0.01	1.5	0.6-3.4	3.3	0.4
Log Interleukin 6 (pg/ml)	2.7	1.7-4.3	16.6	0.0001	3.1	1.9-4.9	22.3	0.0001
Day 8								
Log Presepsin (pg/ml)	2.6	1.5-4.3	12.7	0.0001	4.5	2.0-10.4	17.2	0.0001
Log Interleukin 6 (pg/ml)	3.1	1.6-6.1	11.5	0.001	3.5	1.5-7.8	12.3	0.003

Hazard ratios were standardized to describe the HR for a biomarker change per log unit increase.

Conclusions – Presepsin (1)

- correlated with creatinine, inflammatory biomarkers, duration of ICU treatment and with APACHE II score.

- Levels of presepsin were higher in non-survivors compared to survivors.

- Reveals valuable diagnostic capacity for stages of sepsis severity compared to PCT, IL-6, CRP, WBC in patients being treated on an internal ICU.

- Diagnostic cutoffs of presepsin were set at ≥ 530 pg/ml for Sepsis, at ≥600 pg/ml for severe sepsis and ≥ 700 pg/ml for septic shock.

Conclusions – Presepsin (2)

- **Presepsin levels revealed valuable prognostic capacity to predict short- and long-term all-cause mortality at 30 days and 6 months compared to PCT, CRP, WBC, SOFA and APACHE-II score.**

- **IL-6 revealed comparable prognostic value to presepsin levels.**

- **Diagnostic and prognostic capacity of presepsin was consistenly demonstrated throughout day 1,3 and 8 of ICU-treatment.**

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