TIME IS SURVIVAL

PRESEPSIN: The Sepsis Biomarker
A short monograph

- *Automated quantitative POC method*
- *From just 100 µl whole blood or plasma in 15 minutes*
- *For earlier antibiotic treatment and monitoring of effectiveness*
- *Superior prognostic value for risk assessment*
- *Excellent performance demonstrated in numerous studies*
- *Multi marker testing with other analytes is possible*

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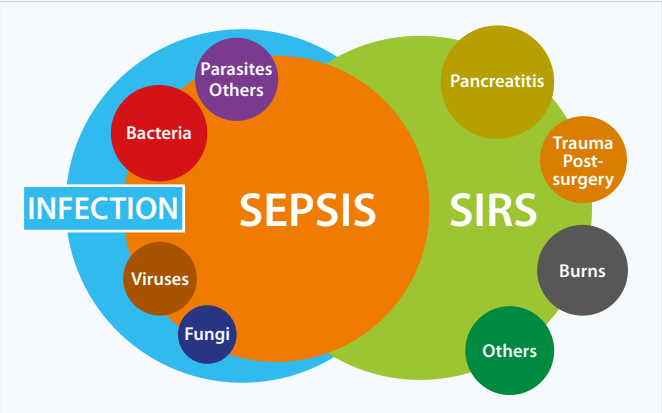
Sepsis

Sepsis is a complex whole-body inflammatory state caused by severe infection by bacteria, fungi or other micro-organisms. Severe sepsis is accompanied by single or multiple organ dysfunction or failure, often leading to death. Cytokines and other substances of the innate immune system are released into the blood to combat the infection. This results in a systemic inflammatory state with formation of thrombi, bleeding and leaky vessels. It proceeds finally in impaired blood flow which damages the organs by depriving them of nutrients and interferes with oxygen supply.

The severity of organ damage and sepsis is often estimated from clinical risk stratification scores such as the Sequential Organ Failure Assessment (SOFA) Score[1], APACHE II („Acute Physiology and Chronic Health Evaluation II") [2], or MEDS (Mortality in Emergency Department Sepsis).[3]



Systemic inflammatory response syndrome (SIRS)	The systemic inflammatory response is manifested by two or more of the following conditions: (1) Body temperature < 36 °C or > 38 °C (hypothermia or fever) (2) Heart rate >90 beats per minute (3) Respiratory rate >20 breaths per minute (tachypnea or hypocapnia due to hyperventilation) (4) White blood cell count < 4,000 cells/mm^3 or > 12,000 cells/mm^3
Sepsis	SIRS in response to a confirmed infectious process. Infection can be suspected or proven.
Severe sepsis	Sepsis with organ dysfunction, hypoperfusion, or hypotension.
Septic shock	Sepsis with arterial hypotension or hypoperfusion and abnormalities in spite of adequate fluid resuscitation.

Definition of different stages in sepsis[4]

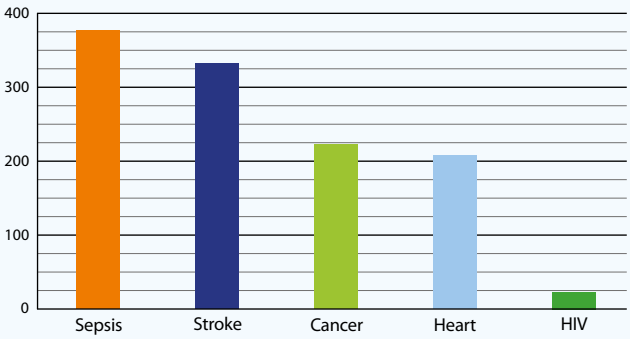
Mortality and Morbidity

Death is common among sepsis patients, with a large proportion dying within the first month of diagnosis.[5] Mortality in patients with severe sepsis can be up to more than 50%.[6] Survivors are often strongly disabled and require long rehabilitation treatment.[7] Especially elderly survivors of severe sepsis are up to three times as likely to develop persistent cognitive and functional impairments.[8]

Sepsis incidence and costs increase dramatically

More than 18 Mio cases of severe sepsis are reported worldwide each year. Incidence increases strongly with a rate of 1.5%/year [9]. Hospitalizations for sepsis have more than doubled over the last 10 years [10]. Sepsis occurs in 1–2% of all hospitalizations and accounts for as much as 25% of intensive-care unit (ICU) bed utilization. Recent US data suggest the annual cost of hospital care for patients with septicemia is USD 14 billion.[11] Incidence and cost aspects seem to be even worse in Europe.[12]

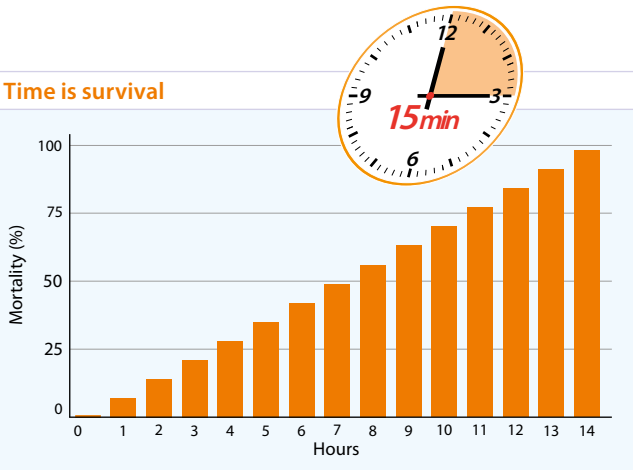
Sepsis cases per 100.000 population (EU/US)

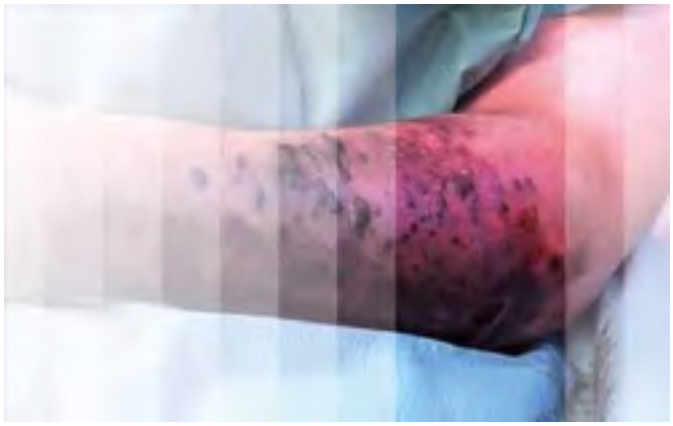


Diagnosis of sepsis: time is survival

About 20-40% of sepsis patients develop sepsis already outside the hospital. The mainstay of sepsis treatment is a rapid diagnosis and early goal directed therapy [13]. By the time physicians realize a patient is septic, it can be too late for starting therapy with broad-range antimicrobials, IV fluids, medication for stabilizing the circulation, and other steps.
Clinical symptoms such as increased pulse, or breathing rate, raised body temperature or laboratory parameters such as white blood cell count or lactate have only limited specificity. About one third of patients with severe sepsis do not show positive blood cultures.[14] And with current methods results would take too long anyhow. Every hour delay in the administration of appropriate antibiotic therapy there is an associated 7% rise in mortality.[15] The problem of increased bacterial resistance is problematic, prolonging length of stay and duration of mechanical ventilation. Therefore also the monitoring any therapeutic measures that have been taken is highly important.
A rapid and reliable test for detection of sepsis and its differentiation from SIRS that is applicable directly in the ICU and that allows monitoring is a major step forward.

Time is survival



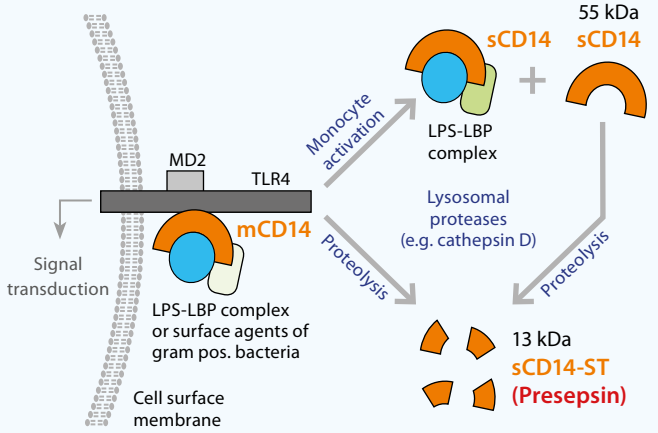


Presepsin: the innovative early biomarker for sepsis

Presepsin is a specific 13 kDa fragment derived from CD14, a 55 kDa membrane glycoprotein of monocytes, macrophages and polymorph nuclear neutrophils. CD14 serves as a receptor for complexes of bacterial lipopolysaccharides (LPS) and LPS binding protein (LPB). It can bind to peptidoglycan and other surface structures in both Gram-positive and Gram–negative bacteria.[16]

CD14 and LPS/LPB complexes activate the toll-like receptor 4 (TLR4, CD 284) specific pro-inflammatory signaling cascade inducing a series of signal transduction pathways that result in a systemic inflammatory response.

Tentative mechanism of Presepsin secretion



mCD14: membrane CD14; sCD14: soluble CD14; sCD14-ST: soluble CD14 subtype (=Presepsin); LPS: lipopolysaccharide; PG: polyglycan, LBP: lipopolysaccharide binding protein, TLR4: toll-like receptor 4; MD2: Co-Protein of TLR4.

The fragment soluble CD14 (sCD14) is shed from the cell membrane into the circulation where it is further fragmented by proteases such as cathepsins to sCD14 subtype (sCD14-ST) or Presepsin[17]. In healthy persons, Presepsin is only found in very low concentrations. However, in patients with sepsis, direct involvement of bacterial LPS and probably phagocytosis, increased values of Presepsin are found already at a very early stage, even before IL-6 rises.[18,19] The plasma half live has been reported to be 4-5h.[6]

Measurement of Presepsin

Presepsin can easily be measured from whole blood or plasma with the compact PATHFAST™ analyzer at the point of care or in the lab.[20] The PATHFAST™ Presepsin immunoassay is based on chemiluminescence and shows excellent precision. The fully automated procedure takes just 15 minutes.

It requires only 100 µl of EDTA- or heparin-anticoagulated blood, or the respective plasma thereof. This makes the method ideal also for pediatric samples. In whole blood samples, the effect of hematocrit is automatically corrected. There is excellent agreement between whole blood and plasma results.[20,24]

Running a test on PATHFAST™ is very simple and does not require special operator skills. Reliable results at the point of care are a prerequisite for patient risk stratification and initiation of immediate targeted therapy.

In addition to Presepsin, PATHFAST™ offers several other STAT assays with relevance in sepsis such as D-Dimer, NT-proBNP, HS-CTnI, or CK-MB. All assays are provided in economical pre-calibrated unit-dose cartridges. Up to six samples can be tested in parallel in one run.

Step 1	Insert cartridge
Step 2	Load sample tube (whole blood or plasma)
Step 3	Press „START“ Result in 15 min

Normal range

The normal range of Presepsin in healthy adults is usually very low with values up to around 320 pg/ml (upper reference limit stated by the manufacturer).[20] Similar values were found in several other studies.[24,35] In a small study the mean Presepsin blood level in 26 preterm newborns was 643 and a median value of 578 pg/ml.[21]

However, there is evidence that in elderly patients or patients with impaired renal function (which is frequently found in elderly patients) there is an increase of values, at least in patients that had no signs of infections.[22] This may be related to bioaccumulation of Presepsin (13 kDa) due to reduced nephrotic mass, similar as described for Procalcitonin (PCT).[23] Therefore interpretaton of results should consider the actual renal function of the patient. In a rabbit cecal ligation and puncture (CLP) model, along with occurrence of blood bacteria, Presepsin levels were elevated even earlier than IL-6, and much earlier than PCT, with a peak at about 3h after onset of the infection and a decline after 4-8 hours.[19] In survivors, Presepsin declines after a few hours whereas it remains elevated in those who died.

Presepsin is a specific and early diagnostic biomarker for sepsis

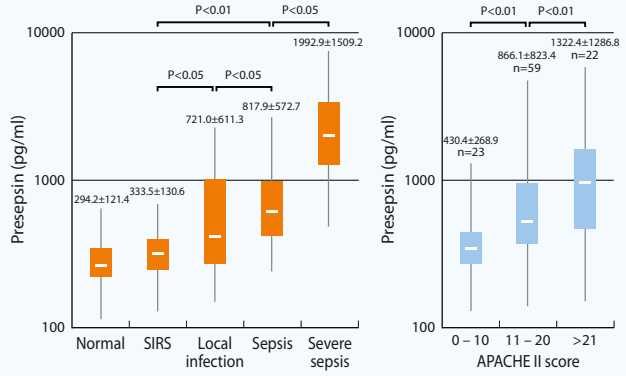
The levels of Presepsin are significantly higher in septic patients than in patients with SIRS or apparently healthy individuals. This has been demonstrated in several recent studies in various countries, and various groups of patients, and in infections cause by either Gram-positive or Gram-negative infections or mixed infections.[18,24,25,26,27,28,29,30,31,32,33,34,35,36,37]

The following table summarizes recent studies in which Presepsin has been often compared with other biomarkers.

Patients	Results (AUC- values of ROC curves)	Conclusions	Reference
859 consecutive patients with at least two criteria for SIRS	Presepsin: 0.784 PCT: 0.680 Presepsin in combination with APACHE II score: 0.858 Presepsin in combination with MEDS score: 0.875	Presepsin is effective and superior over PCT. Combination of Presepsin with clinical scores enhances the diagnostic efficacy.	Liu et al, 2014[28]
226 patients with SIRS (37 with positive and 189 with negative blood culture)	Presepsin: 0.750 at 729 pg/ml, NPV: 94.4% PCT: 0.787 CRP: 0.602	Presepsin is significantly higher in patients with bacteremia and may be useful for ruling out bacteremia in patients with SIRS.	Romualdo et al, 2014[39]
106 patients, in two hospitals in Turin with suspected sepsis or septic shock	Presepsin: 0.701 PCT: 0.875 Mean Presepsin values were significantly in non survivors (60 day mortality) than in survivors. No correlation of between PCT and survival.	Presepsin is useful in the early diagnosis of infection and showed a significant prognostic value. Initial values were significantly correlated with in-hospital mortality of patients affected by sepsis, severe sepsis or septic shock.	Ulla et al, 2014[30]
27 patients with burns	Presepsin: 0.834 PCT: 0.847 CRP: 0.819 WBC: 0.508	Presepsin had comparable performance as PCT in burn patients.	Madenci et al, 2014[34]
30 patients with SIRS and 30 patients with sepsis	Discrimination of SIRS from sepsis: Presepsin: 0.996 PCT: 0.912 CRP: 0.857 WBC: 0.777	Presepsin values were significantly higher in patients with sepsis than the SIRS group. Presepsin was a significantly sensitive indicator of sepsis and useful marker for the rapid diagnosis of sepsis.	Vodnik et al, 2014[35]
207 suspected sepsis patients, multicentric study	Presepsin: 0.908, (cut-off value at 600 pg/ml) PCT: 0.905 (cut-off at 500 ng/ml)	Presepsin and PCT are similar efficient.	Endo et al, 2012[31]
140 patients with suspected sepsis	Presepsin: 0.878 APACHE II: 0.815 PCT: 0.668 Presepsin values increased significantly in the first 72 hours in patients with poor outcome, while values decreased in survivors	Presepsin is efficient in the diagnosis and risk stratification of sepsis.	Spanuth et al, 2012[26]
41 patients	Presepsin: 0.908, (cut-off value at 415 pg/ml) PCT: 0.652 (cut-off at 500 ng/ml) CRP: 0.815 IL-6:0.672	Presepsin is superior over PCT, CRP and IL-6.	Shoshuzima et al, 2011[24]
231 SIRS and sepsis patients	Presepsin: 0.817 PCT: 0.744	Presepsin is efficient.	Yaegashi et al, 2005[18]

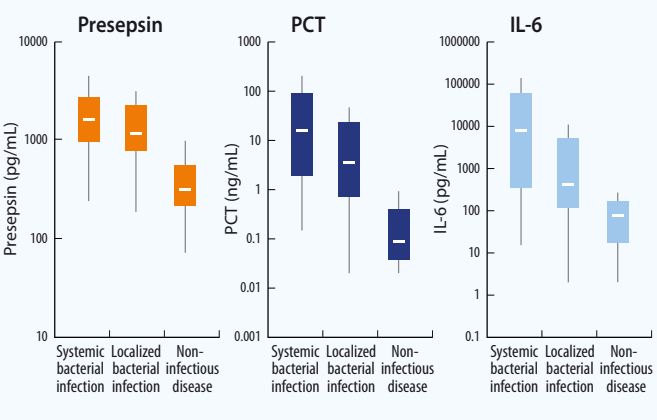
Presepsin and severity of the septic process

Shozushima et al found in a group of patients with signs of SIRS that the concentration of Presepsin was 333.5 pg/mL in the SIRS group, 721 pg/mL in the local infection group, 817.9 pg/mL in the sepsis group, and 1992.9 pg/mL in the severe sepsis group. The blood concentration of Presepsin among the groups increased sequentially.

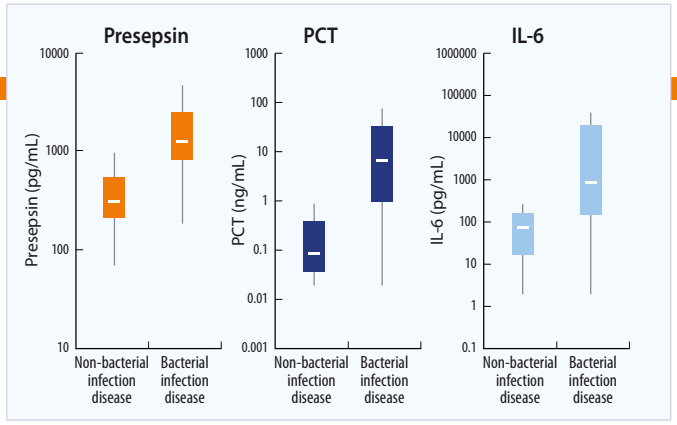


Staging the severity of sepsis with Presepsin (Shozushima et al, 2011)

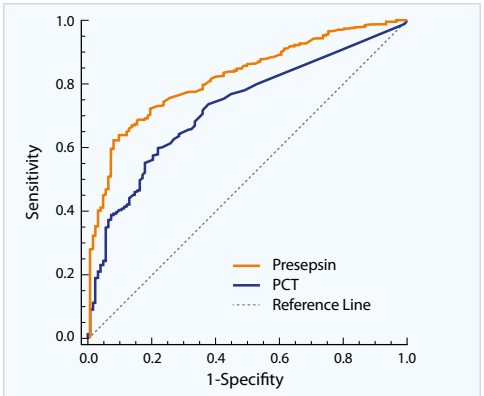
Though blood culture is not always positive in sepsis patients, it is still the gold standard to compare the performance of sepsis biomarkers. In a study with patients with either Gram-positive or Gram-negative bacterial or with fungal infections with positive blood cultures, Presepsin levels were only significantly different between sepsis/infections and severe infections groups, respectively. Presepsin levels reflected the blood culture test and the severity of the clinical course more than other biomarkers such as IL-6 or PCT. A ROC-curve analysis showed superior performance of Presepsin over PCT and for both markers a clearly superior performance over IL-6.[38]



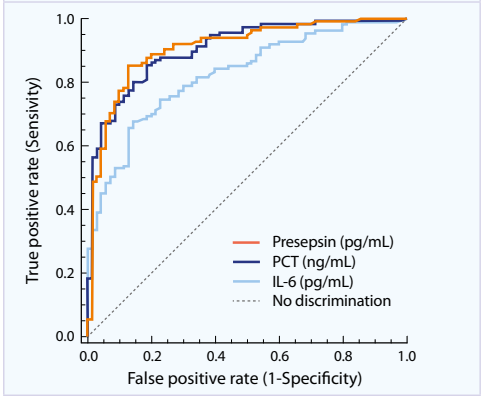
Comparison of Presepsin, PCT and IL-6 in patients with systemic infection, localized bacterial infections, and noninfectious diseases.



There is a clear difference between Presepsin levels in bacteremia and non-bacterial infections, more than with other biomarkers such as PCT or IL-6. (Endo et al, J infect Chemotherap 2012)



ROC curve analysis of 185 patients with or without bacterial infections for the diagnosis of sepsis.

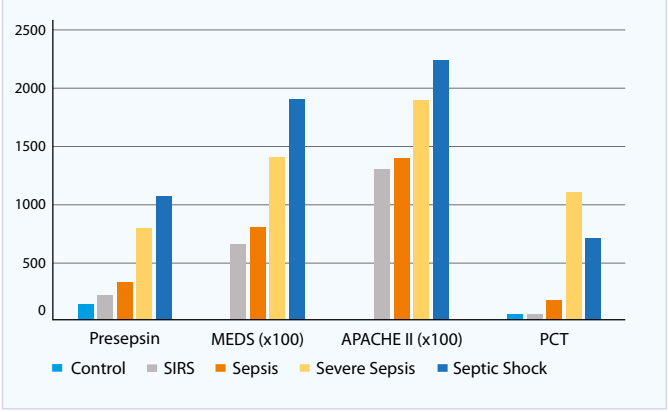


ROC curve analysis of various biomarkers and clinical scores for predicting severe sepsis. (Endo et al, J infect Chemotherap 2012)

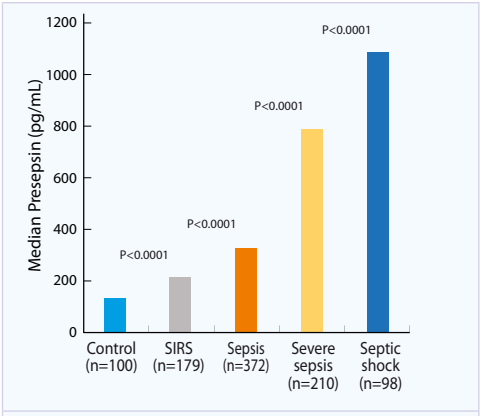
A large study with 859 consecutive patients admitted to the emergency unit with at least two criteria for a systemic inflammatory response investigated the relationship between the Presepsin levels at admission in the emergency department with the severity of disease.

A clear relationship between Presepsin levels and the different stages of sepsis severity was found while for PCT a major increase of concentration is only seen in the most severe form of septic shock. The ROC analysis showed a higher AUC value for Presepsin (0.84) as compared to PCT (0.741) or the clinical scores such as MEDS (0.818), or APACHE II (0.744). Combing of either score with Presepsin slightly enhanced the predictive power of Presepsin alone. Therefore Presepsin can be used for early risk stratification and for early decision for targeted therapy when required. A drop of Presepsin during the course of sepsis may show, at least to some extent, a response to successful therapy and hence the test may have potential as a monitoring tool.[28]

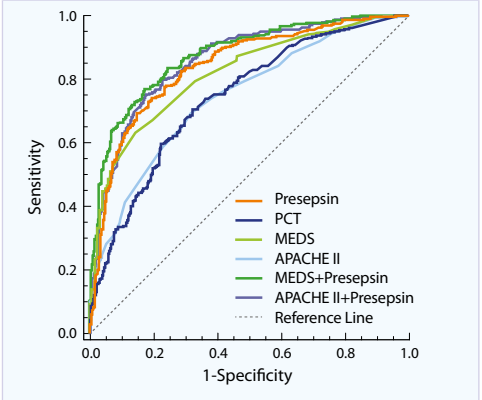
Biomarkers and clinical scores



Relationship between sepsis biomarkers and clinical scores. The clinical score values were tentatively multiplied by 100 in order to get a comparable scale, PCT is shown in pg/ml.



Presepsin levels and severity of sepsis on admission.



ROC-curves of various markers, clinical scores or combination. (Liu et al, Crit Care 2013)

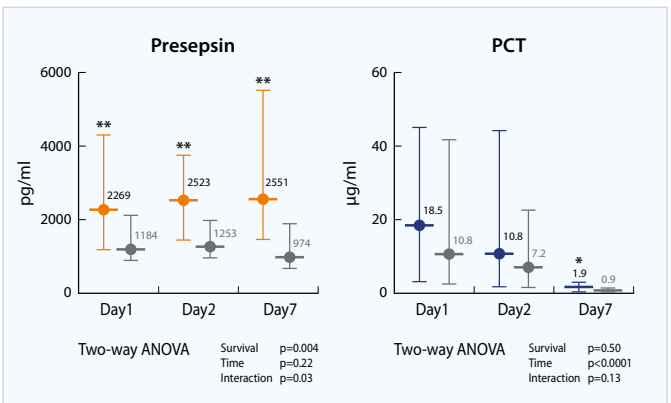
A Spanish study investigated the performance of Presepsin as a predictor of bacteremia for the early detection of blood-stream infections in 226 patients admitted to the emergency department with SIRS.A negative predictive value for Presepsin of 94.4% was found when using a cut-off valueof 729 pg/ml.[39]

Presepsin as a predictor for infections in surgery

Novelli et al evaluated the analytical and clinical performance of the PATHFAST Presepsin assay system for early diagnosis of infection in 70 adult patients, including 35 cadaveric organ transplant recipients and 35 abdominal surgery patients with a mean age of 56.1 years. Presepsin was tested at 48 hours after surgery together with blood cultures and demonstrated 100% sensitivity to show the presence of infection, confirmed by positive blood cultures.[29]

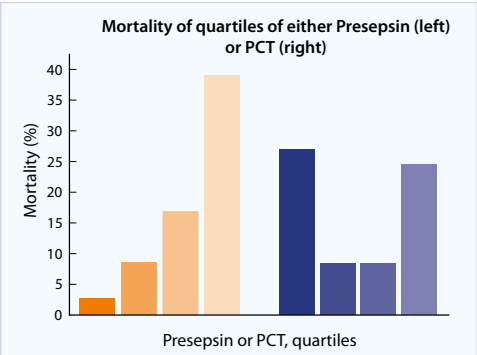
Presepsin as a prognostic marker

In a study in Italy on 100 patients with sepsis (50 decedents and 50 survivors), the level on day 1 and the evolution of Presepsin levels over time was significantly higher in decedents than in survivors whereas PCT was not different in the two groups except from day 7. Presepsin was the only variable independently associated with ICU and 28-day mortality and showed better prognostic accuracy than PCT in the range of SOFA score (area under the curve (AUC) from 0.64 to 0.75 vs. AUC 0.53 to 0.65).[40]

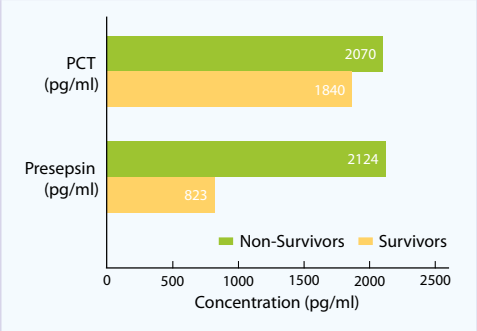


Comparison between Presepsin (left) and PCT (right) in patients with severe sepsis or septic shock. (Masson et al, Crit Care 2014)

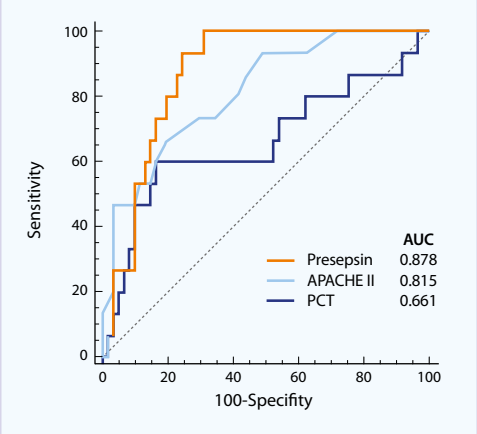
A German study on 140 patients admitted to the emergency department with signs or suspicion of sepsis showed a clear and statistically highly significant (p<0.0001) relationship between Presepsin concentrations and mortality, while this relationship was not found for PCT. The median Presepsin values at admission for survivors was 823 pg/ml and 2124 pg/ml (p<0.0001) for non survivors whereas the PCT values showed no significant difference (p=0.7452) with 1.84 ng/ml and 2.07 ng/ml. A ROC curve analysis showed superior prognostic accuracy for Presepsin as compared to PCT, and addition of Presepsin to the clinical APACHE II score could increase the AUC-value from 0.815 to 0.905. Improvements of adding Presepsin also other clinical scores was shown as well, e.g. for MEDS from 0.819 to 0.936. The negative predictive value of Presepsin alone was 98.5% (PCT: 92.4%), showing a high potential to rule out sepsis with a single assay.



Presepsin values and mortality



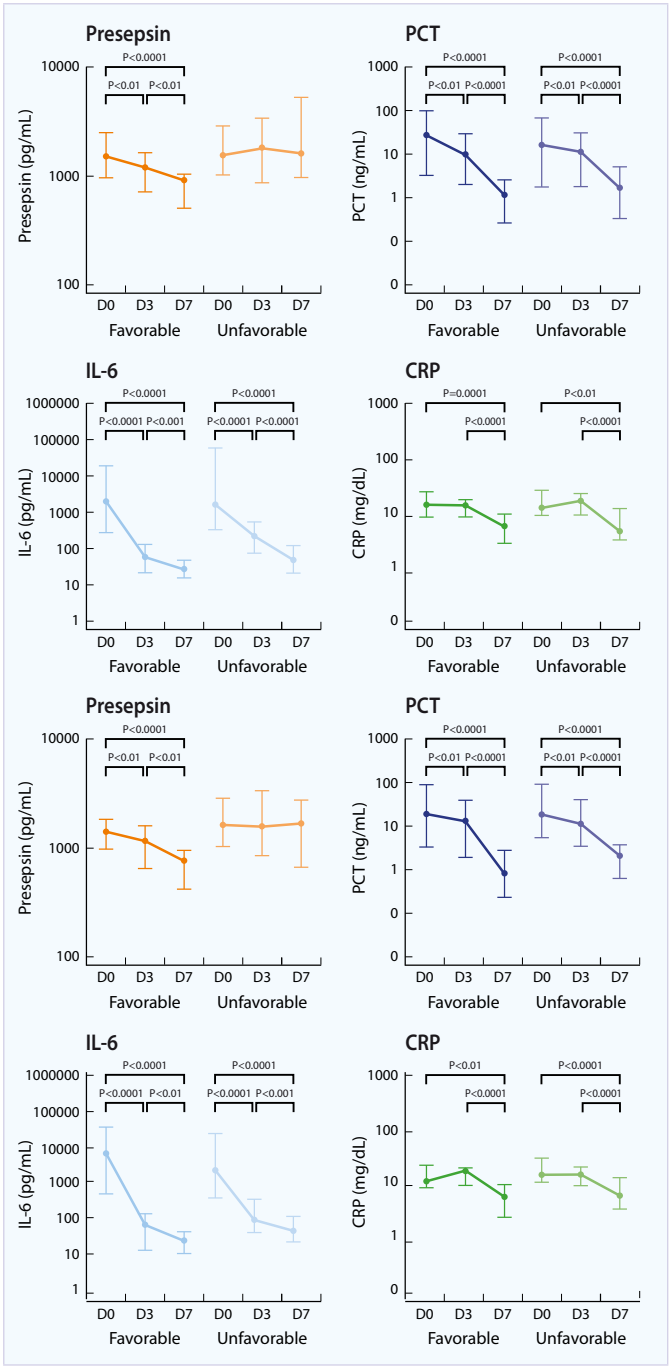
Median values (Presepsin and PCT, both in pg/ml) of survivors and non survivors (adapated from Spanuth et al 2012)



ROC-curve analysis

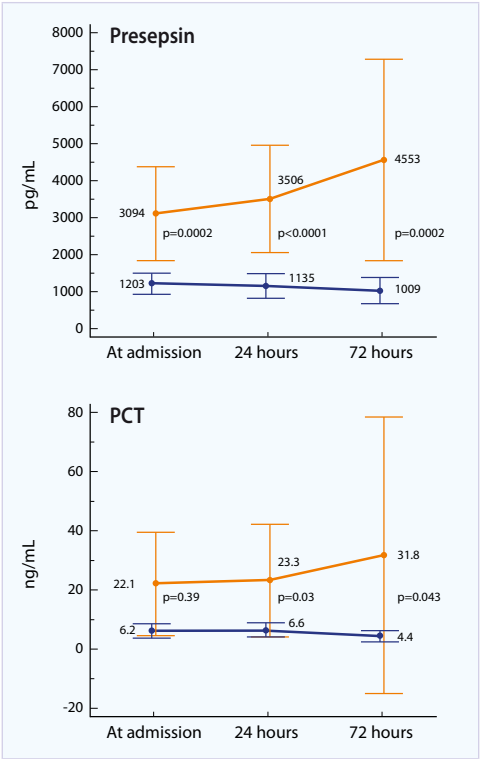
Presepsin and Monitoring

In a recent multicentric study Presepsin and other biomarkers used in sepsis were investigated in sepsis patients over the clinical course. All markers declined over time in patients with predicted favorable outcome according to SOFA or APACHE II score. Unlike other biomarkers, only Presepsin values showed a tendency to stay elevated in the group of patients with unfavorable outcome.[41]



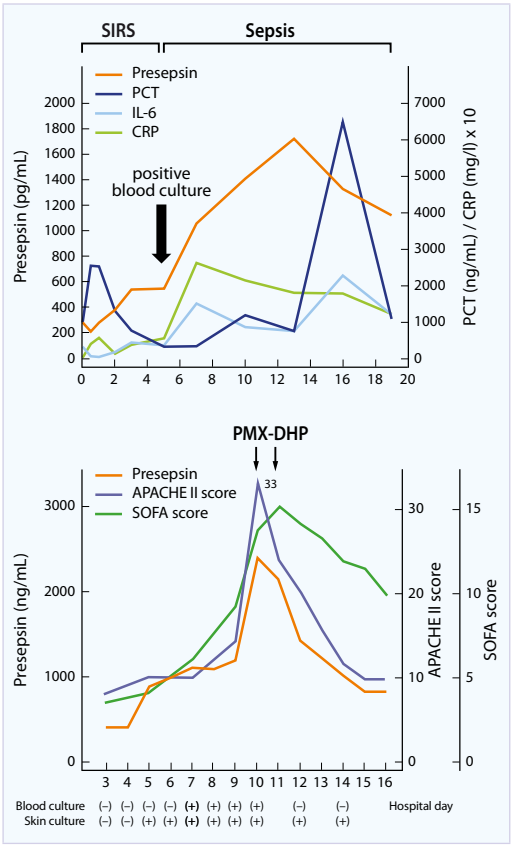
Course of biomarkers over time in sepsis patients with favorable or unfavorable outcome according to SOFA (L) or APACHE II scores (R). Presepsin values are in the upper left panel, respectively.

A clear difference in the development of Presepsin and PCT values during the course of treatment could be demonstrated in 140 patients with sepsis who got anti-microbial treatment after diagnosis of sepsis. Presepsin showed a clear trend towards lower values in survivors over the period from 0 - 72 h observation time while non-survivors reached very high values. In contrast, PCT though also much higher in non survivors showed only a marginal decline over time in the survivors.



Course of mean values of Presepsin and PCT (error bars: 95% CI) in non survivors (30 days, red line) and survivors (blue line). (Spanuth E et al, 2012)

The specific advantage of Presepsin over other biomarkers becomes also visible from time courses of individual patients.
Therefore Presepsin is a parameter that helps to guide therapy in sepsis.



Time course of a burn patient (Shozushima et al, 2011, L) and of an elderly patient who developed a septic shock after trauma and was treated with polymixin-B-immobilized fiber direct hemoperfusion (Endo et al, 2012)

Sepsis and disseminated intravascular coagulation

A large proportion of sepsis patients develops severe, sometimes lethal coagulation problems. In a study in which 11 biomarkers were tested in 82 patients with suspected sepsis admitted to the emergency unit, an optimal panel of markers for the detection of disseminated coagulation (DIC) and sepsis was the combination of Presepsin and protein C with an AUC– value of 0.913 for sepsis and 0.88 for DIC.[42]

Conclusions

- **Presepsin is a reliable, specific and sensitive biomarker for sepsis and is a valuable tool for the very early diagnosis of sepsis by Gram-positive and Gram-negative bacteria and probably fungi.**
- **Presepsin rises earlier than other biomarkers and does not show unspecific increases, e.g. by trauma.**
- **Presepsin values help to stratify the severity of the septic disease with excellent correlation to APACHE II and SOFA scores, respectively.**
- **Presepsin exceeds the prognostic power of other sepsis biomarkers and is specifically useful when combined with clinical risk scores.**
- **The time course of Presepsin can be used for monitoring: a decline demonstrates response to therapy and predicts a favorable outcome.**

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