



Biomarkers and sepsis

The contribution of procalcitonin (PCT) and interleukin-6 (IL-6) to sepsis management

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CH-6343 Rotkreuz
Switzerland
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Sepsis represents a significant medical burden

Sepsis is a potentially life threatening complication of infection, trauma or burn injury. It remains one of the leading causes of death around the world and is a primary cause of mortality from infection.^{1,2}

The first indication of possible sepsis is systemic inflammatory response syndrome (SIRS), a condition defined by the presence of two or more clinical indicators (Figure 1). Sepsis is defined as SIRS with evidence or suspicion of infection and if one or more organs become dysfunctional it is defined as severe sepsis. The patient is said to be in septic shock when sepsis is accompanied by refractory hypotension/hypoperfusion.³

The mortality rate of sepsis is very high and increases depending on the stage and severity of the sepsis; 24 % of patients with SIRS die, increasing to over 50% of patients with septic shock (Figure 2).²

Sepsis is a leading cause of death around the world.

I. Confirmation of infection

Diagnosis of an infection on the basis of microbiological evidence or clinical criteria

II. Systemic inflammatory host response (SIRS) (at least 2 criteria)

- Fever ($\geq 38^{\circ}\text{C}$) or hypothermia ($\leq 36^{\circ}\text{C}$) confirmed by rectal, intravascular or intravesical measurement
- Tachycardia: heart rate ≥ 90 bpm
- Tachypnea (frequency $\geq 20/\text{min}$) or hyperventilation ($\text{PCO}_2 \leq 4.3$ kPa/ ≤ 33 mmHg)
- Leukocytosis ($\geq 12,000/\text{mm}^3$) or leukopenia ($\leq 4,000/\text{mm}^3$) or $\geq 10\%$ immature neutrophils in differential blood count

III. Acute organ dysfunction (at least 1 criterion)

- Acute encephalopathy: reduced alertness, disorientation, agitation, delirium
- Relative or absolute thrombocytopenia: decrease in platelet counts by more than 30% within 24 hours or a platelet count of less than $100,000/\text{mm}^3$. Thrombocytopenia due to acute hemorrhage or immunological causes must be ruled out
- Arterial hypoxemia: $\text{PaO}_2 \leq 10$ kPa (≤ 75 mmHg) while breathing ambient air or a $\text{PaO}_2/\text{FiO}_2$ ratio of ≤ 33 kPa (≤ 250 mmHg) on oxygen administration. A clinically manifest heart or lung disease must be ruled out as a cause of hypoxemia
- Renal impairment: diuresis of ≤ 0.5 mL/kg/h for at least 2 hours despite adequate volume resuscitation and/or an increase in serum creatinine level to $>$ twice the upper limit of normal (ULN)
- Metabolic acidosis: Base excess of ≤ -5 mmol/L or lactate concentration of $>1.5 \times \text{ULN}$

Sepsis: criteria I and II

Severe sepsis: criteria I, II and III

Septic shock: criteria I and II, as well as a systolic arterial blood pressure of ≤ 90 mmHg for at least 1 hour, or mean arterial pressure of ≤ 65 mmHg, or the necessity of vasopressor administration to maintain a target systolic arterial pressure of ≥ 90 mmHg or mean arterial pressure of ≥ 65 mmHg. Hypotension persists despite adequate volume resuscitation and cannot be explained by other causes

Figure 1: Clinical indicators of SIRS/sepsis and organ-specific markers (from the Guidelines of the German Sepsis Society).⁴

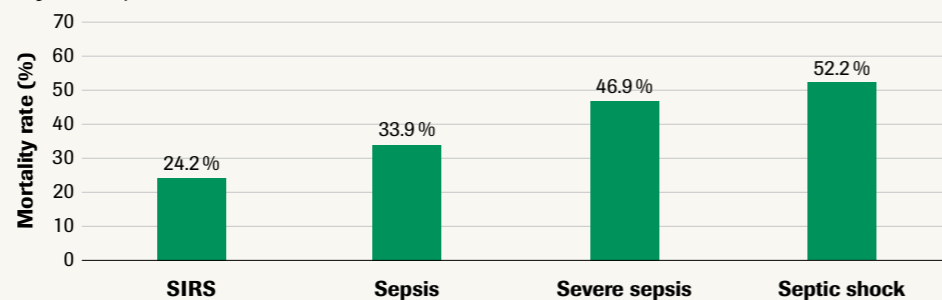


Figure 2: The four categories of inflammatory response to infection are associated with a significant increase in mortality.²

Diagnosis of sepsis – Time matters

Clinical signs suggestive of sepsis are non-specific, making diagnosis of sepsis difficult.⁵ Blood cultures remain the gold standard for diagnosis of patients with suspected sepsis, however, they have several limitations:^{6,7}

- Require up to 5 days to obtain the results
- Lack sensitivity
- Easy to contaminate
- Cannot assist in early sepsis management decisions

Timely diagnosis and initiation of effective antibiotic treatment and sepsis management has been shown to improve patient outcomes. Almost 80% of patients with severe sepsis survive if treatment is initiated within 1 hour of diagnosis. Survival declines rapidly if treatment is delayed further, dropping to only 42% if initiated 6 hours after diagnosis.⁸ In addition, it is desirable to prevent unnecessary antibiotic usage in order to reduce treatment costs, reduce the risk of adverse drug reactions and to slow the spread of antibiotic-resistant bacteria.^{9,10}

Biomarkers in sepsis

There is considerable unmet medical need in sepsis, and biomarkers may have an important clinical role to play (Figure 3). Biomarkers can indicate the presence of sepsis, differentiate bacterial from viral or fungal infection, differentiate local from systemic infection, stratify severity of sepsis, may help to guide antibiotic therapy, provide prognostic information, evaluate response to therapy, predict septic complications and predict the development of organ dysfunction. However, the exact role of biomarkers is yet to be defined.⁵

Diagnosis and differential diagnosis of infection

- Infection vs non-infection⁵
- Infection type (bacterial, viral, fungal)⁵
- Systemic or local⁵

Recognition and stratification of severity of sepsis⁵

Early and appropriate decision regarding antibiotic therapy decisions

- Initiation, and discontinuation of antibiotics^{9,11}

Figure 3: Unmet medical needs in the management of sepsis and suspected sepsis.

Timely diagnosis and treatment of sepsis to improve patient survival.

Interleukin-6 (IL-6)

IL-6 is an early marker for inflammation in sepsis

IL-6, a key mediator for inflammation and an early alarm signal of infection that becomes elevated as part of the inflammatory response, has emerged as a valuable biomarker in the management of sepsis.¹²

IL-6 levels predict development of septic complications

In a study of 1,032 patients with severe trauma, patients who subsequently developed septic complications had the highest IL-6 levels on day 1 following injury.¹⁴ Similarly, in a study of 50 patients following major surgery, IL-6 levels were correlated with the development of septic complications during the first 5 days following surgery (area under the curve [AUC] 0.82; 95% CI: 0.66 – 0.98), with a sensitivity of 90% and selectivity of 58% (Figure 5). Furthermore, when IL-6 levels and clinical indicators were combined, sensitivity and selectivity increased to 100% and 79%, respectively.¹⁵

IL-6 levels predict severity of sepsis

Early peak IL-6 levels correlate significantly with the development of SIRS and sepsis. The degree of elevation in IL-6 levels can be used to differentiate SIRS from severe sepsis and septic shock, with higher IL-6 levels correlating with increased severity (Figure 4).¹⁶

IL-6 levels are associated with patient outcome and organ dysfunction

As a marker for systemic inflammation, high IL-6 levels may be predictive of future organ dysfunction.¹² In addition, continually elevated IL-6 levels have been reported to be predictive of mortality in patients with sepsis (Figure 5).¹⁶

IL-6 is a key mediator for inflammation and an early alarm signal of infection.

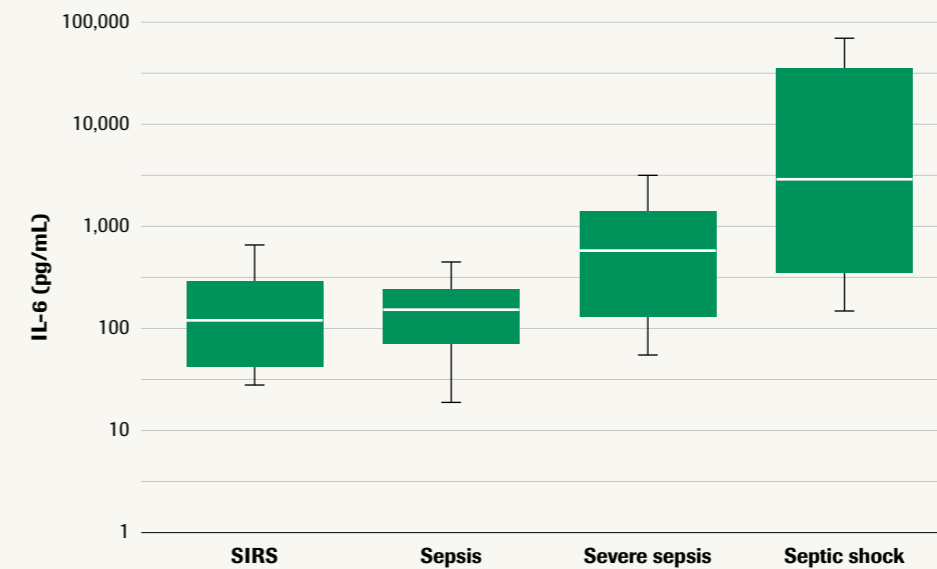


Figure 4: Differentiation between SIRS, sepsis, severe sepsis and septic shock by IL-6. Plasma IL-6 levels in patients with SIRS (n = 18), sepsis (n = 14), severe sepsis (n = 21), and septic shock (n = 25). Data are presented as box plots with line representing the median, the box limits the 25th and 75th percentiles, and the error bars the 10th and 90th percentiles.¹⁶

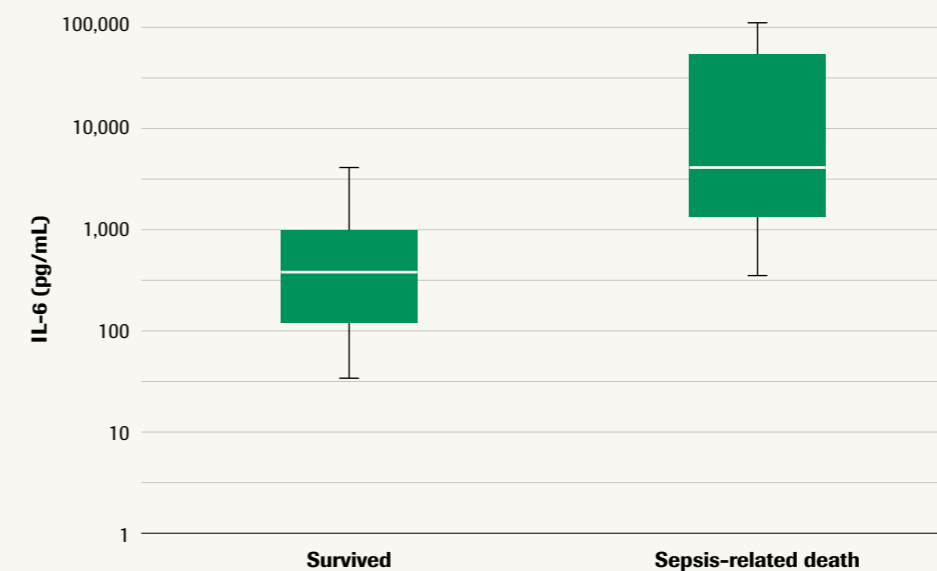


Figure 5: IL-6 plasma levels in patients who survived (n = 38) or who died (n = 18) of sepsis-related causes. Data are presented as box plots with line representing the median, the box limits the 25th and 75th percentiles, and the error bars the 10th and 90th percentiles.¹⁶

Procalcitonin (PCT)

Physiological role of PCT

PCT is a propeptide of calcitonin¹², produced by parafollicular cells of the thyroid¹⁷ and neuroendocrine cells of the lung and intestine.¹⁸ PCT levels are raised in response to bacterial endotoxins and proinflammatory stimuli, including IL-6, interleukin 1- β (IL-1 β) and tumour necrosis factor- α (TNF- α).¹¹ PCT has been reported to be a sensitive marker for bacterial infection, with especially high levels being present following an infection of bacterial origin.¹⁹ Conversely, interferon- γ (IFN- γ) blocks the production of PCT, resulting in low PCT levels following viral infection.¹¹

PCT can aid in the diagnosis and stratification of sepsis

Evidence supports a value for PCT in differentiating patients with sepsis caused by bacterial infection from those with SIRS due to a non-infectious cause. By combining PCT with clinical indicators, the accuracy of sepsis diagnosis may be improved further (Figure 6).¹⁶ PCT levels increase as sepsis progresses and severity increases, allowing the differentiation of patients with SIRS, sepsis, severe sepsis or septic shock (Figure 7).¹⁶ Furthermore, PCT levels correlate with increased organ dysfunction in patients with sepsis (as measured by the Sequential Organ Failure Assessment [SOFA] score)¹³, and are increased in patients with poorer outcome. For example, in a study of 78 patients with sepsis, PCT levels 48 hours after admission were significantly lower in patients who subsequently survived compared with those who died.¹⁶

PCT levels increase as sepsis progresses and severity increases, allowing the differentiation of patients with SIRS, sepsis, severe sepsis or septic shock.

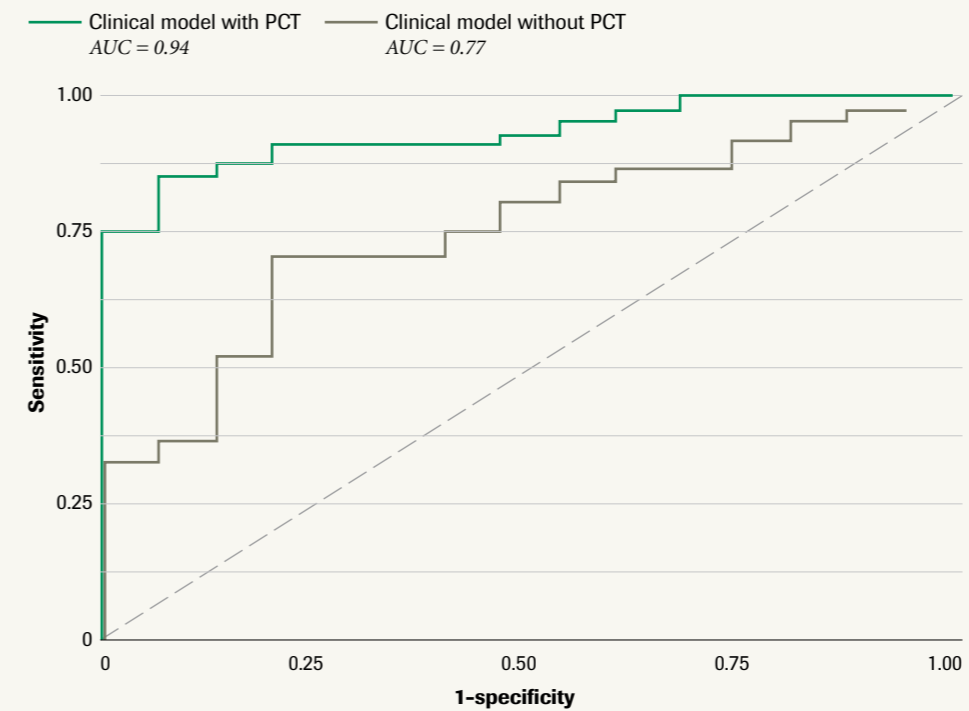


Figure 6: Accuracy of sepsis diagnosis based on a clinical model with and without PCT in 78 consecutive patients admitted with acute systemic inflammatory response syndrome (SIRS) and suspected infection. PCT increased the AUC value for the routine value-based model from 0.77 (CI, 0.64 to 0.89) to 0.94 (CI, 0.89 to 0.99; $p = 0.002$).¹⁶

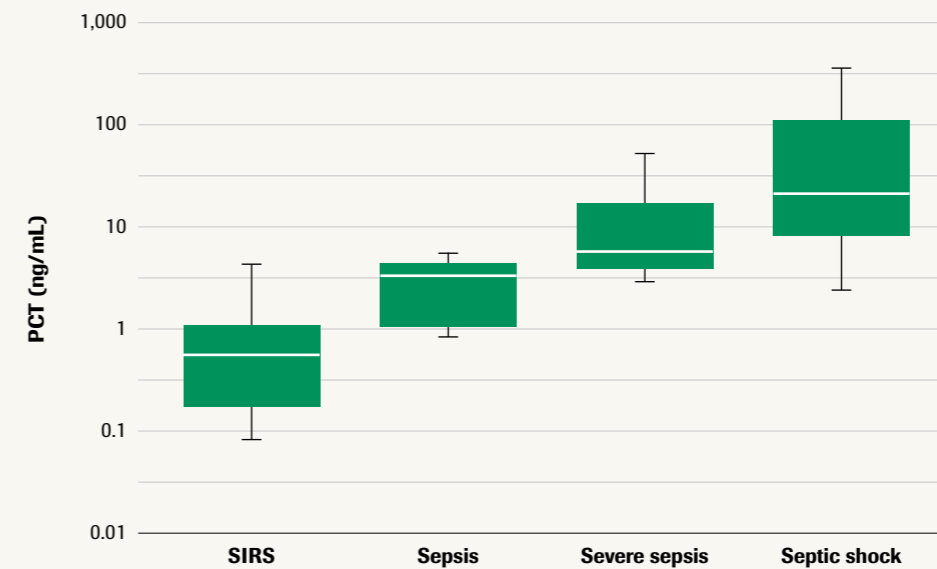


Figure 7: Differentiation between SIRS, sepsis, severe sepsis and septic shock by PCT. Plasma PCT levels in patients with SIRS ($n = 18$), sepsis ($n = 14$), severe sepsis ($n = 21$), and septic shock ($n = 25$) indicates that increased PCT levels correlate with increased severity of condition. Data are presented as box plots with dots representing the median, the box limits the 25th and 75th percentiles, and the error bars the 10th and 90th percentiles.¹⁶

PCT levels as a tool for antibiotic therapy guidance

Effective antibiotic treatment is reflected by declining PCT values. Consequently, serial determinations of PCT can be used to monitor the course of systemic bacterial infections and to tailor therapeutic interventions more efficiently.¹¹

In multiple studies in various conditions, the use of PCT to guide antibiotic therapy not only reduced the mean number of days of antibiotic treatment, but also reduced the number of days within the intensive care unit (and thereby costs), with no detrimental effect on patient outcome (Figure 8). Algorithms have been developed that use PCT levels as a basis for recommendations regarding antibiotic therapy, both upon admission to the intensive care unit and during subsequent daily follow-up (Table 1).²⁰

Use of PCT to guide antibiotic therapy reduces antibiotic usage and length of stay in ICU.

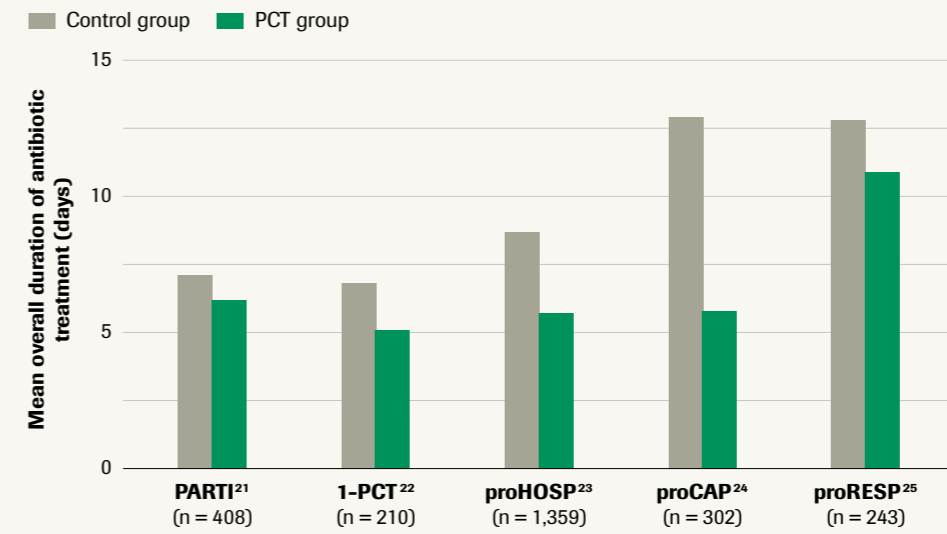


Figure 8: In five studies, the use of PCT-guided treatment algorithm reduced the duration of antibiotic treatment in patients with bacterial respiratory tract infections.²¹⁻²⁵

Proposed for evaluation at admission:

PCT (µg/L)	<0.25	<0.50	≥0.50	>1.0
Antibiotic initiation:	Strongly discouraged	Discouraged	Encouraged	Strongly encouraged

*Exception: empirical therapy recommended in all patients with clinical suspicion of infection

Proposed for follow-up evaluation every 1 to 2 days:

PCT (µg/L)	<0.25 (or drop >90%)	<0.50 (or drop >80%)	≥0.50	>1.0
Antibiotic discontinuation:	Strongly encouraged	Encouraged	Discouraged	Strongly discouraged

*Exception: consider continuation of antibiotics if patients are clinically unstable

Table 1: Proposed PCT-directed algorithm for initiation or discontinuation of antibiotic therapy for high acuity/risk patients in intensive care setting. The algorithm was developed based on a meta-analysis including 14 randomised controlled trials (4,467 patients total).²⁰

Other biomarkers

C-reactive protein

CRP is an acute phase protein that is elevated as part of the inflammatory response, and is a later marker for sepsis than IL-6 or PCT (Figure 9).^{13,14,26}

Lactate

Lactate levels are elevated in septic patients as a result of poor lactate clearance, and are associated with an increased likelihood of infectious complications, an extended stay in the intensive care unit (Figure 12), and increased mortality.¹⁴ Current guidelines suggest that reducing lactate to ≤ 1.5 mmol/L correlates with an increased survival rate.⁴

Glucose

Both hypo- and hyperglycemia have been found to correlate with increased mortality.²⁷ Current guidelines suggest that lowering glucose levels to below 150 mg/dL may be considered in septic ICU patients.^{4,28} Glucose variability is also a prognostic factor for hospital mortality in septic patients, with greater glucose variability coupled with low glucose levels correlating with an increased risk of death.²⁹

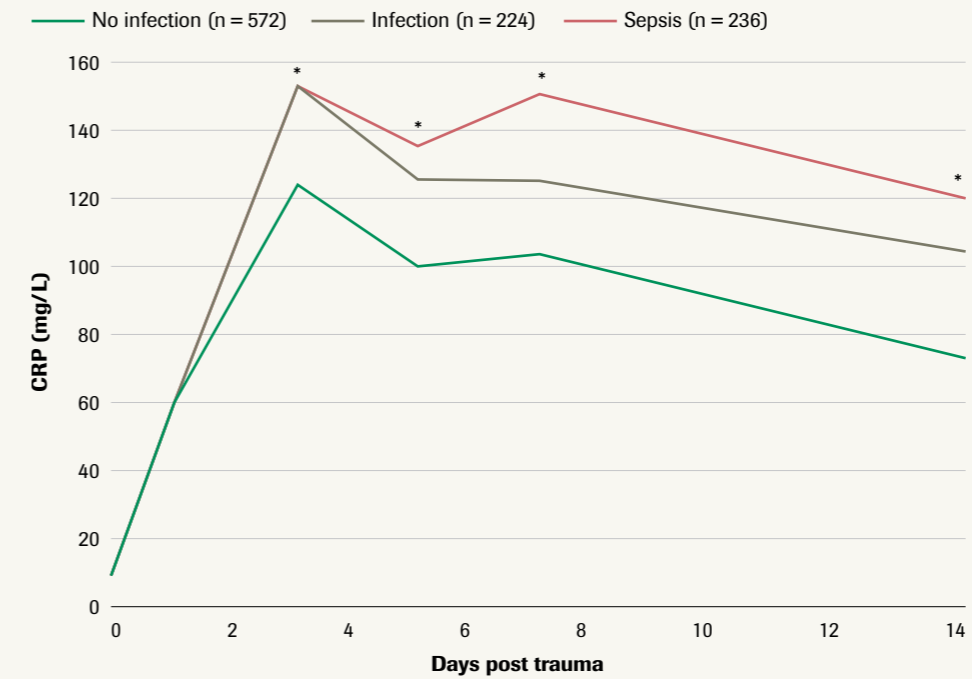


Figure 9: CRP levels are elevated in sepsis patients several days after trauma.

* $p < 0.01$ vs no-infection group.¹⁴

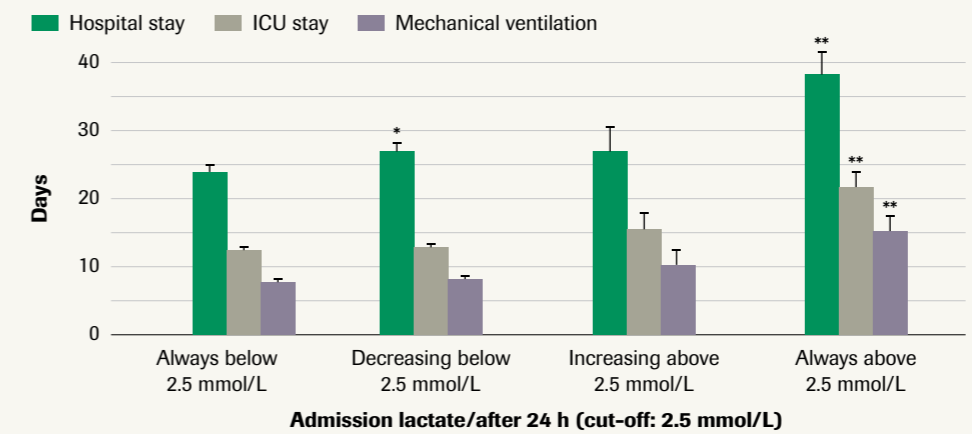


Figure 10: Association between 24-hour lactate clearance and length of hospital stay, ICU stay, and length of mechanical ventilation.

* $p < 0.05$ vs “always below 2.5 mmol/L” group. ** $p < 0.0001$ vs “always below 2.5 mmol/L” group.

$n = 1,032$ patients.¹⁴

Use of biomarkers in combination

IL-6, PCT and CRP are complementary biomarkers that provide different information throughout the course of sepsis (Figures 11 and 12). IL-6 levels increase rapidly following insult and peak at around 2–6 hours in surgical trauma patients.¹³ Following insult, IL-6 stimulates expression of acute phase proteins such as CRP³⁰ and induces PCT production through the immune response cascade.^{11,31} PCT levels increase primarily in the presence of a bacterial infection, and raised PCT levels are highly suggestive of bacterial sepsis. CRP is a later marker of inflammation, with levels peaking 12–48 hours after infection.¹³

The combination of PCT and IL-6 has been shown to have greater sensitivity and specificity for the detection of early-onset neonatal sepsis than either marker alone.^{32,33} The use of a biomarker panel has the potential to provide greater information than measurement of single markers alone and should be investigated further.^{5,16,34}

The use of a biomarker panel has the potential to provide greater information than measurement of single markers alone.

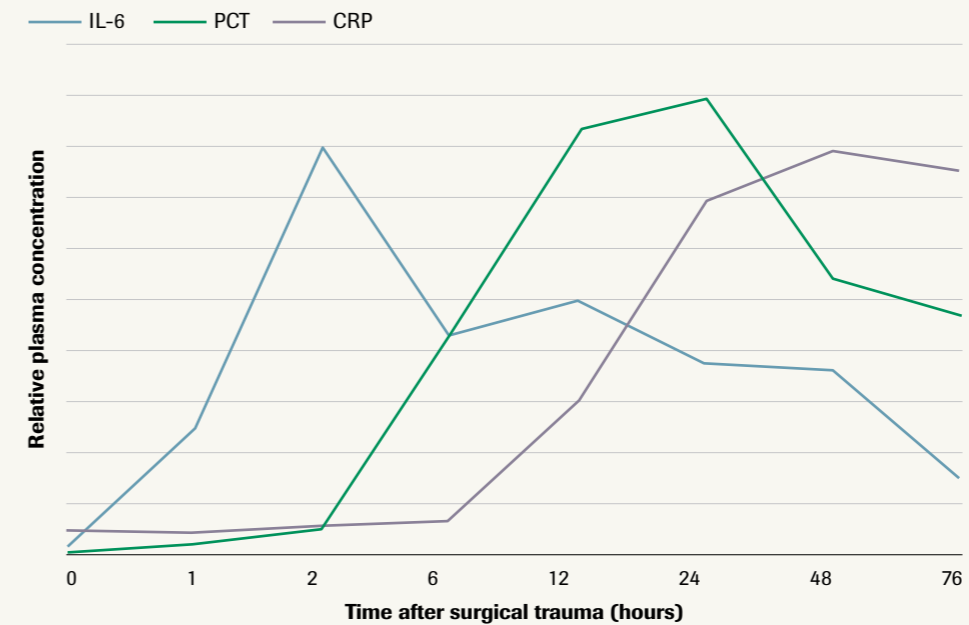


Figure 11: IL-6, PCT and CRP have distinct kinetic profiles following bacterial infection in patients who have undergone thoracic surgery.¹³

IL-6

- Early mediator and indicator of inflammatory response, infection and sepsis
- Indicative of inflammation and infection earlier than blood cultures
 - IL-6 levels elevated within 2 hours of insult
- Increased levels correlate with increased sepsis severity and decreased survival

PCT

- Acute phase protein primarily raised during bacterial infection
- PCT levels can drive treatment algorithm for initiation, modification and discontinuation of antibiotics
 - Elevated within 6 hours of insult, and highly suggestive of bacterial sepsis
- Indicative of infection earlier than blood cultures
- Can differentiate between sepsis and severe sepsis

CRP

- Late marker for inflammation, infection and sepsis
- Confirms increases in IL-6 and PCT to aid diagnosis of sepsis

Figure 12: Complementary role of IL-6, PCT and CRP in the management of sepsis.

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