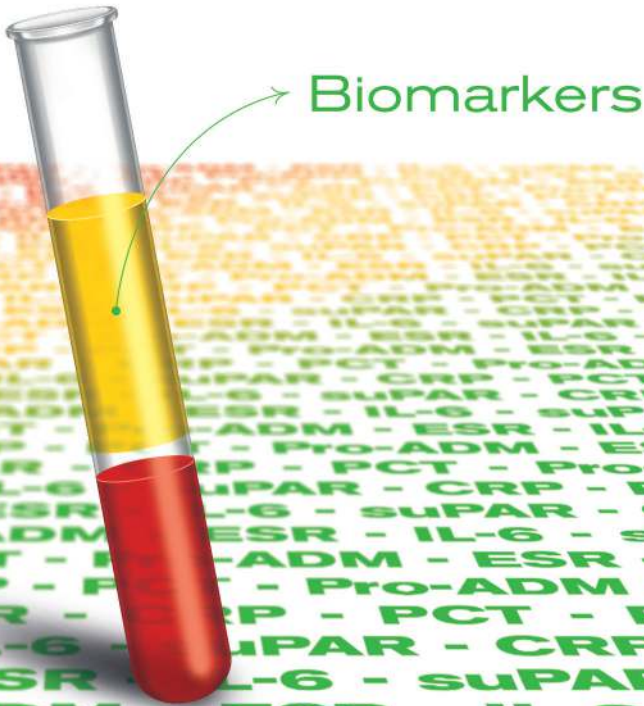


# Inflammatory Biomarkers For Clinical Use



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## Introduction

The use of biomarkers in clinical research and clinical practice has become a big part of the patient risk assessment. Biomarkers are a measure used to monitor and predict health states in individuals or across populations so that the appropriate therapeutic intervention can be planned.

A wide range of biomarkers are used today. Many of these biomarkers are relatively easy to measure and are an important part of the routine medical examinations. Examples of biomarkers include both pulse and blood pressure measures as well as more complex laboratory tests of blood and tissues. The key issue at hand is determining the relationship between any given measurable biomarker and the relevant clinical endpoints.

In the following we will address six biomarkers in more detail; suPAR, CRP, PCT, Pro-ADM, ESR, and IL-6, which are used as routine biomarkers for immune and inflammation status in acute medical patients.

Biomarker	Primary use	Disease specific	Diagnostic value	Prognostic value	Stability	Time to result
suPAR	Health status and risk stratification	No				
CRP	Diagnosis of serious bacterial infections based on inflammation	No				
PCT	Diagnosis of bacterial infection and sepsis	Yes				
Pro-ADM	Diagnosis and prognosis of sepsis – and continuous monitoring of sepsis	Yes				
ESR	Marker for inflammation	Yes				
IL-6	Marker for inflammation, such as lupus or rheumatoid arthritis, or infection, like sepsis.	No				
Risk scoring systems (e.g. DEPT, NEWS)	Provide predicted mortality information about patients	No				

## suPAR

**What is suPAR?** suPAR is an unspecific inflammatory biomarker of immune activation.

suPAR (soluble urokinase Plasminogen Activator Receptor) is the soluble form of the cell membrane-bound protein uPAR, which is expressed mainly on immune cells, endothelial cells, and smooth muscle cells. uPAR is released during inflammation or immune activation. The suPAR level, therefore, reflects the extent of immune activation in the individual.<sup>1</sup>

**What is suPAR used for?** Knowledge of the overall health status of the patient. suPAR can assist in the decision of discharge or admission of patients.

**What does suPAR tell you?** suPAR provides information on whether disease is present or not, as well as the seriousness of the disease. Elevated suPAR levels are associated with the presence and progression of disease and with an increased risk of mortality.<sup>2</sup> suPAR reflects the level of chronic inflammation, and is therefore a potential marker for the development of diseases.<sup>3,4</sup>

**When is suPAR elevated?** The suPAR level is elevated by diseases in general, and is not diagnostic for a specific disease. Hence, a suPAR is a good marker for rule out of disease.

The suPAR level discriminates non-survivors from survivors. suPAR levels range from health blood donor levels of 2-3 ng/ml<sup>5</sup> to critical ill patients with levels often above 10 ng/mL<sup>4,6</sup>, often seen for liver and kidney failure.

**Why use suPAR in clinical routine?** suPAR predicts the risk of readmission and mortality in unselected acute medical patients. The suPAR level reflects the degree of disease burden and prognosis of the patient. A low suPAR level is suggestive of discharging the patient, whereas a high suPAR level indicates disease and risk of readmission and mortality. suPAR has a strong negative predictive value for ruling out disease.<sup>7</sup>

**What is the stability of suPAR?** The suPAR blood level is stable with no diurnal variation and no changes following fasting. The level increases and decreases with progression and improvement of a disease, respectively.

<sup>1</sup> Thunø M, et al. *Dis Markers*. 2009;27(3):157-72

<sup>2</sup> Rasmussen LJH, et al. *Emerg Med J* 2016;33:769–775

<sup>3</sup> Eugen-Olsen, J. et al. *J. Intern. Med.* 2010;268, 296–308

<sup>4</sup> Donadello K, et al. *J Crit Care*. 2014 Feb;29(1):144-9

<sup>5</sup> Hastrup E, et al. *PLoS One* 2014, e110555.

<sup>6</sup> Koch A, et al. *Liver Int* 2014; 34:1330–1339

<sup>7</sup> Rasmussen LJH, et al. *Crit Care Med*. 2018 Dec;46(12):1961-1968

## CRP

**What is CRP?** CRP is a non-specific indicator of inflammation and one of the most sensitive acute phase reactants.

CRP (C-reactive protein) is a protein made by the liver in response to bacterial proteins. It is found in blood plasma, whose circulating concentrations rise in response to inflammation. CRP is released into the blood within a few hours after an injury, the start of an infection, or other causes of inflammation.<sup>8,9</sup>

**What is CRP used for?** CRP is used to detect inflammation due to acute conditions or to monitor the severity of disease in chronic conditions.<sup>8</sup>

**What does CRP tell you?** CRP is mainly used as an infection and inflammation marker.

The CRP level provides information on whether inflammation is present or not, without identifying the source of the inflammation.<sup>8</sup>

**When is CRP elevated?** Higher levels are found in mild inflammation and viral infections (10–40 mg/L), active inflammation and bacterial infection (40–200 mg/L), severe bacterial infections (>200 mg/L).<sup>10</sup>

**Why use CRP in clinical routine?** To diagnose bacterial infection based on the patients' medical history, signs, and symptoms. This is particularly useful for inflammation problems as CRP levels drop as inflammation decreases or after surgery to ensure that the patient is free of post-surgery infection.<sup>8</sup>

**What is the stability of CRP?** It is an acute-phase protein which increases following interleukin-6 secretion by macrophages and T cells.<sup>9</sup> There is a high day to day variability in CRP levels making CRP levels unreliable as a marker of chronic inflammation.

<sup>8</sup>. <https://labtestsonline.org/tests/c-reactive-protein-crp>

<sup>9</sup>. Thompson D. et al, 1999. *Structure*. 7 (2): 169–77

<sup>10</sup>. Chew KS, 2012. *Journal of Emergencies, Trauma, and Shock*. 5 (2): 115–7

## PCT

**What is PCT?** PCT (Procalcitonin) is a peptide precursor of the hormone calcitonin. PCT is produced by many types of cells in the body, often in response to bacterial infections but also in response to tissue injury.

**What does PCT tell you?** PCT is a biomarker for the diagnosis of sepsis, severe sepsis, and septic shock.<sup>11,12</sup>

**What is PCT used for?** Detection of or rule out of sepsis in seriously ill patients.<sup>12</sup>

**When is PCT elevated?** In response to a pro-inflammatory stimulus, especially of bacterial origin. The induction period for procalcitonin ranges from 4–12 hours with a half-life spanning from 22–35 hours. It does not rise significantly with viral or non-infectious inflammations.<sup>11</sup>

**Why use PCT in clinical routine?** To distinguish between bacterial and non-bacterial causes of infections. PCT is normally measured for (1) to confirm or exclude a diagnosis of sepsis, severe sepsis, or septic shock, (2) to assess the severity and to follow up on systemic inflammation, and (3) to guide personal antibiotic therapy and focus treatment. High PCT levels have a high positive predictive value to rule in the diagnosis of sepsis. Normal or very low PCT plasma concentrations have a high negative predictive value to rule out severe systemic inflammation or sepsis but not as high as suPAR.<sup>11-13</sup>

**What is the stability of PCT?** The lag time for PCT induction is approx. 2–4 hours after the onset of sepsis, a time period that has usually passed if patients are presented at the emergency department. Peak levels of PCT occur at 24 to 48 hours after sepsis.<sup>11,12</sup>

<sup>11</sup>. Reinhart K, et al. 2000. *Intensive Care Medicine*. 26 (9): 1193–20

<sup>12</sup>. Meisner M, et al (1999). *Critical Care*. 3 (1): 45–50

<sup>13</sup>. Huang Q et al. *Shock*. 2019

## Pro-ADM

**What is Pro-ADM?** The hormone Adrenomedullin (ADM) is expressed by all tissues and organ systems, including cardiovascular, renal, pulmonary, gastrointestinal, and endocrine tissues. It functions as a circulating hormone as well as a local autocrine and paracrine effector.

**What is Pro-ADM used for?** Evaluation of sepsis' diagnosis and prognosis as well as in monitoring these conditions.<sup>14</sup>

**What does Pro-ADM tell you?** Whether or not the patient has a bacterial infection.

**When is Pro-ADM elevated?** High levels have been described in septic patients<sup>15-17</sup>. Elevated levels are not specific as they have also been found in chronic heart failure. The increased level of Pro-ADM is in proportion to disease severity<sup>18-20</sup>

**Why use Pro-ADM in clinical routine?** ADM has a bactericidal activity and could be helpful in the evaluation of sepsis' diagnosis and prognosis and in monitoring such conditions.<sup>14</sup>

**What is the stability of pro-ADM?** ADM is unstable and difficult to measure.

<sup>14</sup>. Hinson JP, et al. *Endocr Rev.* 2000;21:138–167

<sup>15</sup>. Struck J, et al. *Peptides* 2004;25:1369-72.

<sup>16</sup>. Eto T. *Peptides* 2001;22:1693-711

<sup>17</sup>. Nishio K, et al. *Crit Care Med* 1997;25:953-7.

<sup>18</sup>. Jougasaki M, et al. *J Clin Invest* 1996;97:2370–6

<sup>19</sup>. Jougasaki M, et al. *Circulation* 1995;92:286–9

<sup>20</sup>. Nishikimi T, et al. *J Am Coll Cardiol* 1995;26:1424–31

## ESR

**What is ESR?** The erythrocyte sedimentation rate (ESR) is a blood test that measures how quickly erythrocytes (red blood cells) settle at the bottom of a test tube. Normally, red blood cells settle relatively slowly. A faster-than-normal rate may indicate inflammation in the body.<sup>22-24</sup>

**What is ESR used for?** An ESR test can help determine if you have a condition that causes inflammation. This may include arthritis, vasculitis, or inflammatory bowel disease. An ESR may also be used to monitor an existing condition.

The ESR is not diagnostic, it is a non-specific test. It provides general information about the presence or absence of an inflammatory condition.<sup>22,23</sup>

**What does ESR tell you?** An ESR does not specifically diagnose any diseases, but it can provide information about whether or not there is inflammation in your body.

A higher than normal ESR may be related to an inflammatory condition, such as: Infection, Rheumatoid arthritis, rheumatic fever, Vascular disease, Inflammatory bowel disease, Heart disease, Kidney disease, Certain cancers.<sup>22,23</sup>

A slower than normal ESR may indicate a blood disorder, such as: Polycythemia, Sickle cell anemia, Leukocytosis, an abnormal increase in white blood cells.

A moderate ESR may indicate pregnancy, menstruation, or anemia, rather than an inflammatory disease.<sup>23</sup>

**When is ESR elevated?** In the presence of inflammation.

**Why use ESR in clinical routine?** If your results are not in the normal range, it doesn't necessarily mean you have a medical condition that requires treatment.

The ESR is typically used in conjunction with other tests, such as C-reactive protein.<sup>22</sup>

<sup>22</sup>. Hinkle J, et al. p. 267–68.

<sup>23</sup>. <https://labtestsonline.org/understanding/analytes/esr/tab/test/>

<sup>24</sup>. [https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=erythrocyte\\_sedimentation\\_rate](https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=erythrocyte_sedimentation_rate)

## IL-6

**What is IL-6?** Interleukin-6 (IL-6) is a protein produced by various cells. It helps to regulate immune responses, which makes the IL-6 test potentially useful as a marker of immune system activation. IL-6 is a cytokine and helps the immune system to direct the body's immune response.<sup>25</sup>

IL-6 acts on a variety of cells and tissues. It promotes differentiation of B-cells (white blood cells that produce antibodies), promotes cell growth in some cells, and inhibits growth in others. It stimulates the production of acute phase proteins.

**What is IL-6 used for?** IL-6 may help to evaluate a person who has a condition associated with inflammation, such as lupus or rheumatoid arthritis, or with infection, such as sepsis. It may also be used in the evaluation of diabetes, stroke, or cardiovascular disease.<sup>25</sup>

**What does IL-6 tell you?** An elevated IL-6 may mean that the person tested has an inflammatory condition. IL-6 is a nonspecific marker associated with an inflammatory response, and is not diagnostic for any specific disease or disease process.<sup>25</sup>

**When is IL-6 elevated?** IL-6 can be elevated with inflammation, infection, autoimmune disorders, cardiovascular diseases, and some cancers. Elevated concentrations of IL-6 must be interpreted within the clinical context of the patient. Normally, IL-6 is not detected in the blood or is present in low levels. Normal concentrations of IL-6 do not exclude the possibility of an ongoing inflammatory process (< or = 1.8 pg/m).<sup>25</sup>

**Why use IL-6 in clinical routine?** The usefulness of the IL-6 test in the medical setting is still being established. The goal is to determine whether IL-6 is causing or contributing to disease states. This will show how it may be used to help in the diagnosis, treatment, and monitoring of diseases. It may be used to help guide treatment or even as a target for the treatment of these conditions.<sup>25</sup>

**What is the stability of IL-6?** IL-6 has limited stability. Following centrifugation, plasma must be either immediately frozen or refrigerated. Samples can only be stored at refrigerated temperatures for 24 hours, after which time samples must be frozen. Storage of plasma for any length of time at room temperature is not acceptable.<sup>26</sup>

<sup>25</sup>. <https://labtestsonline.org/tests/interleukin-6>

<sup>26</sup>. <https://www.mayocliniclabs.com/test-catalog/Clinical+and+Interpretive/63020>

## What are the biomarkers a measure for?

**suPAR:** Immune activation in response to inflammation.

A measure of the individuals' health status with a high NPV.<sup>7</sup> The suPAR level is associated with morbidity and mortality and is elevated across diseases.<sup>27-30</sup>

**CRP:** Bacterial infection.

Used mainly as an inflammation marker. Relatively low levels of CRP are found during viral infections compared to bacterial infections.<sup>31</sup>

**PCT:** Bacterial infection.

Low levels may indicate no bacterial infection, but a viral infection.

High levels indicate a high probability of sepsis or meningitis.

**Pro-ADM:** Bactericidal activity.

Helpful in the evaluation of sepsis' diagnosis and prognosis and in monitoring such conditions.<sup>14</sup>

**ESR:** Presence or absence of an inflammatory condition.<sup>23,24</sup>

**IL-6:** Useful as a marker of immune system activation.<sup>25</sup>

<sup>7</sup>. Rasmussen LJH, et al. *Crit Care Med.* 2018 Dec;46(12):1961-1968

<sup>14</sup>. Hinson JP, et al. *Endocr Rev.* 2000;21:138-167

<sup>27</sup>. Huang Q et al. *Shock.* 2019

<sup>28</sup>. Lyngbaek S, et al. *The American journal of cardiology* 2012;110:1756-63.

<sup>29</sup>. Raggam RB, et al. *Journal of internal medicine* 2014;276:651-8.

<sup>30</sup>. Reichsoellner M, et al. *Journal of clinical microbiology* 2014;52:4063-6.

<sup>31</sup>. Enocsson H, et al (2009). *Arthritis and Rheumatism.* 60 (12): 3755-60

<sup>23</sup>. <https://labtestsonline.org/understanding/analytes/esr/tab/test/>

<sup>24</sup>. [https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=erythrocyte\\_sedimentation\\_ratex](https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=erythrocyte_sedimentation_ratex)

<sup>25</sup>. <https://labtestsonline.org/tests/interleukin-6>



## When are the biomarkers elevated?

**suPAR:** In chronic inflammation or immune activation.<sup>1</sup> High suPAR is associated with multimorbidity and progression of disease. One in eight patients have a suPAR above 6 ng/ml, associated with lengthy hospital stay, readmission, and mortality. If suPAR is even higher (>10 ng/ml), liver and kidney failure is often observed.

**CRP:** In serious bacterial infections, such as in sepsis. After trauma or a heart attack, with active or untreated autoimmune disorders. The level of CRP can jump as much as a thousand-fold in response to a bacterial infection.<sup>8</sup>

**PCT:** In a response to a pro-inflammatory stimulus, especially of bacterial origin.<sup>32</sup> It does not rise significantly with viral or non-infectious inflammations.

**Pro-ADM:** In hypertension, chronic renal disease, and heart failure.<sup>18</sup> In the latter its concentrations are increased in proportion to disease severity.<sup>19,20</sup>

**ESR:** In the presence of inflammation.

**IL-6:** In inflammation, infection, autoimmune disorders, cardiovascular diseases, and some cancers. Normally, IL-6 is not detected in the blood or is present in low levels. Normal concentrations of IL-6 do not exclude the possibility of an ongoing inflammatory process (< or = 1.8 pg/m).

<sup>1</sup>. Thunø M, et al. *Dis Markers*. 2009;27(3):157-72

<sup>8</sup>. <https://labtestsonline.org/tests/c-reactive-protein-crp>

<sup>18</sup>. Jougasaki M, et al. *J Clin Invest* 1996;97:2370-6

<sup>19</sup>. Jougasaki M, et al. *Circulation* 1995;92:286-9

<sup>20</sup>. Nishikimi T, et al. *J Am Coll Cardiol* 1995;26:1424-31

<sup>32</sup>. Long SS et al (2012). *Principles and Practice of Pediatric Infectious Diseases* (4th ed).

## When are the biomarkers best used?

**suPAR:** In the assessment of the patient when in doubt of their health status. For risk stratification in unselected patients.

**CRP:** When it is suspected that a serious bacterial infection is present based on the patients' medical history, signs, and symptoms.

**PCT:** When suspecting a bacterial infection and when a guided antibiotic therapy is needed.<sup>33</sup> When to detect or rule out sepsis in a seriously ill person.<sup>12</sup>

**Pro-ADM:** In the evaluation of sepsis' diagnosis and prognosis and in monitoring such conditions.<sup>14</sup>

**ESR:** To detect the presence of inflammation caused by one or more conditions such as infections, tumors or autoimmune diseases; to help diagnose and monitor specific conditions such as temporal arteritis, systemic vasculitis, polymyalgia rheumatica, or rheumatoid arthritis.<sup>23</sup>

**IL-6:** In evaluating a patient who has a condition associated with inflammation, such as lupus or rheumatoid arthritis, or with infection, such as sepsis. It may also be used in the evaluation of diabetes, stroke, or cardiovascular disease. An elevated IL-6 may mean that the person tested has an inflammatory condition. IL-6 is a nonspecific marker associated with an inflammatory response, and is not diagnostic for any specific disease or disease process.

<sup>12</sup>. Meisner M, et al (1999). *Critical Care*. 3 (1): 45-50

<sup>14</sup>. Hinson JP, et al. *Endocr Rev*. 2000;21:138-167

<sup>23</sup>. <https://labtestsonline.org/understanding/analytes/esr/tab/test/>

<sup>33</sup>. Schuetz P, et al. 2011. *BMC Medicine*. 9: 107

## What can we learn from the biomarker measurements?

**suPAR:** Whether disease is present or not and the seriousness of disease. The suPAR level is elevated across diseases, and not solely associated with one specific disease. Therefore, suPAR is applicable as a prognostic marker and not as a diagnostic marker. This characteristic may be utilized for risk stratification in unselected patients.

**CRP:** Information on whether inflammation is present, without identifying the source of the inflammation.

**PCT:** Presence of sepsis or not.<sup>12</sup> Distinguishing between bacterial and non-bacterial causes of infections, such as meningitis and pneumonia.

**Pro-ADM:** In the evaluation of sepsis' diagnosis and prognosis and in monitoring such conditions.<sup>14</sup>

**ESR:** Indication on whether inflammation is present.

**IL-6:** Whether or not an inflammatory condition is present. IL-6 is a nonspecific marker associated with an inflammatory response, and is not diagnostic for any specific disease or disease process.

<sup>12</sup>. Meisner M, et al (1999).Critical Care.3 (1): 45–50

<sup>14</sup>. Hinson JP, et al. Endocr Rev.2000;21:138–167

Biomarker	Feature	Primary use
<b>suPAR</b>	Universal biomarker for <b>inflammation</b> across disease and <b>rule-out of disease</b> . suPAR level is associated with disease severity and mortality	Health status and risk stratification
<b>CRP</b>	Universal biomarker for <b>inflammation</b> caused mostly by bacterial infections, without identifying the source of the inflammation	Diagnosis of serious bacterial infections based on inflammation
<b>PCT</b>	Specific biomarker for diagnosis of <b>meningitis, sepsis, and septic shock</b> caused mostly by bacterial infections	Diagnosis of bacterial infection and sepsis
<b>Pro-ADM</b>	Specific biomarker for diagnosis and prognosis of <b>sepsis</b>	Diagnosis and prognosis of sepsis – and continuous monitoring of sepsis
<b>ESR</b>	Detection of <b>inflammation</b>	Marker for inflammation
<b>IL-6</b>	Detection of condition associated with inflammation	Marker for inflammation

Fig. 1 The six biomarkers often used in routine associated to immune and inflammation status in acute medical patients.





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Code no: M024 V1 2020