

[suPAR]

Monograph

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suPAR – Background

The biomarker 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, and therefore the suPAR level reflects the extent of immune activation in the individual¹. All human beings have a baseline level of suPAR that is individually determined and increases with age.

Studies have shown that the suPAR level is associated with morbidity and mortality in a number of acute and chronic diseases and in the general population²⁻¹⁵. 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.

Originally, uPAR (urokinase plasminogen activator receptor) was proven a receptor for urokinase (uPA) which splits plasminogen into active plasmin. Moreover, uPAR interacts with other proteins and plays a role in several important cell processes like migration, adhesion, angiogenesis, proliferation, and chemotaxis¹.

The suPAR protein was discovered in 1991, when it was found to be a marker of cancer progression¹. In recent years, several studies have shown that suPAR is associated with a number of chronic diseases²⁻¹² (including cardiovascular, hepatic, renal, and pulmonary diseases), and that the level is a predictor of a negative outcome of various infectious diseases¹⁷⁻²¹ (tuberculosis, HIV, malaria, sepsis, meningitis, pneumonia) and in critically ill patients¹⁵.

Across diseases, the suPAR level discriminates non-survivors from survivors. suPAR reflects the level of chronic inflammation, and therefore it has been studied as a potential marker of development of diseases, and studies have shown that an elevated level predicts development of chronic diseases and cancer in the general population^{2,15}.

The suPAR blood level is stable with no diurnal variation and no changes following fasting. suPAR can be measured in blood, plasma, urine, cerebrospinal fluid, ascites fluid and pleural fluid¹. The level increases and decreases with progression and improvement of a disease, respectively, but more slowly compared to e.g. C-reactive protein (CRP).

The normal suPAR plasma level is 2-3 ng/mL in healthy individuals, about 3-4 ng/mL in unselected patients in emergency departments, and about 9-10 ng/mL in critically ill patients.

At Copenhagen University Hospital, Hvidovre in Denmark, suPAR measurement has been implemented as a clinical routine procedure.

For further information, please see appendices and subsequent sections

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suPAR in the general population

The following factors are associated with an **elevated suPAR level**:

- Daily smoking¹⁻⁵
- Obesity³
- Previous AMI³
- Low HDL cholesterol/high LDL cholesterol¹⁻³
- Unhealthy diet³
- Physical inactivity³
- Age^{1-3,5,6}

Moreover, an elevated suPAR level is associated with **future** incidence of:

- Mortality¹
- Cardiovascular diseases^{1,2}
- Cancer^{1,5}
- Type 2 diabetes¹
- Renal failure⁷

In the general population, the suPAR level is higher in **females** than in males; the suPAR levels in young healthy males and females are about 2.5 ng/mL and 3.0 ng/mL, respectively. The suPAR level increases slightly with **age** but, above all, it is affected by **lifestyle and risk factors**. Among lifestyle factors **smoking** is definitely the most important – daily smoking is associated with an increase in suPAR of 1-1.5 ng/mL compared to non-smokers^{1-5,7}.

Moreover, an **unhealthy diet** and, to a lesser extent, **physical inactivity** may also increase the suPAR level³. However, the impact on suPAR is significantly smaller compared to the impact of smoking (about 0.2 ng/mL for an unhealthy diet). The association between alcohol consumption and suPAR is not clear^{2,3,5}, but alcoholic liver disease causes very high suPAR levels⁸.

Cardiovascular risk factors affect the suPAR level, as there is a slightly positive association with LDL-cholesterol and a clearly negative association with HDL-cholesterol¹⁻³. **Previous AMI** causes an increase in suPAR level of about 0.4 ng/mL^{3,7}. Two studies have demonstrated an association between elevated blood pressure and suPAR^{1,2}, but in a third study this could not be confirmed³. A BMI of 20-35 kg/m² has no notable effect on the suPAR level, but in **obesity** (BMI > 40) the suPAR level is about 0.5 ng/mL higher than in normal weight individuals³.

suPAR and future development of diseases

In the general population an elevated suPAR level is associated with future **development of cancer, cardiovascular diseases, and type 2 diabetes** and is a predictor of **premature mortality and renal failure (Figure 1)**^{1,2,5,7}.

Unpublished data from the Danish Inter99 cohort (the cohort in *Haupt et al.*³) show that the mortality risk is associated with the suPAR level itself, and not with the underlying risk factors which cause increased suPAR levels. For example, the mortality risk in non-smokers with a high suPAR level is increased compared to smokers with a low suPAR level. Thus, learning about the individual's risk factors may indicate the reason for an elevated suPAR level, but it still seems that the individual's risk is primarily correlated with the suPAR level.

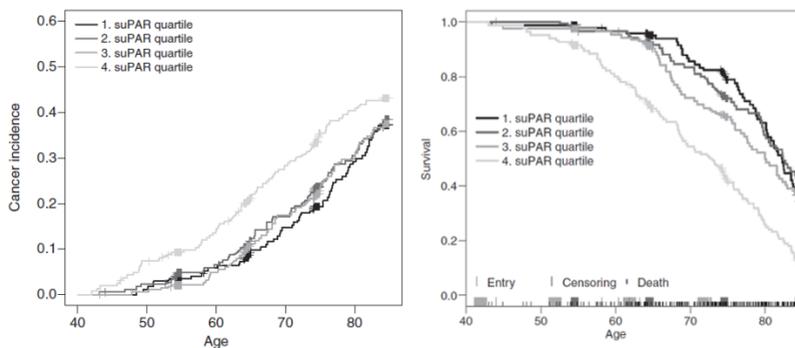


Figure 1. The left graph displays cancer incidence during a 12.6-year follow-up of 2,602 individuals in the Danish MONICA cohort. The suPAR level is below 3.4 ng/mL in the 1st quartile and above 4.9 ng/mL in the 4th quartile. The right graph displays mortality in the 1,310 males in the same study. The suPAR level is below 3.1 ng/mL in the 1st quartile and above 4.7 ng/mL in the 4th quartile. Figure modified from Eugen-Olsen et al., *JIM* 2010.

The overall impact of lifestyle and risk factors on suPAR

Please note that although the single factors mentioned above in general have a very small impact on suPAR, the **overall impact** of a number of risk factors may be considerable. Adjusted analyses show that a 30-year-old non-smoking, and physically active male of normal weight on a healthy diet has a suPAR level of about 2.5 ng/mL, whereas a 30-year-old obese, heavily smoking, and inactive male on an unhealthy diet has a suPAR level of about 5.4 ng/mL³. This exceeds the difference between the 1st and 4th suPAR quartile in Figure 1 and therefore indicates a considerable risk difference.

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suPAR in the emergency department

In the emergency departments, shortened hospital stays and a reduced number of beds cause a large patient turnover. For optimal treatment and observation of patients admitted to the emergency departments, a proper risk assessment is needed to ensure that the most ill patients are prioritized and are quickly examined and put under a more careful observation. Moreover, unnecessary admissions and the complications from these (functional decline, delirium, and iatrogenic infections) are avoided by identifying those patients who can be discharged.

So far, systematized triage systems are used for this risk assessment and to prioritize the order of patients to be treated.

A major proportion of patients admitted to emergency departments are elderly medical patients, including many multimorbid, weak, and frail patients often presenting unspecific symptoms.

Studies from various emergency departments located in the Copenhagen region, Denmark, among others the emergency departments at Hvidovre Hospital, Hillerød Hospital, and Frederiksberg Hospital, have shown that suPAR is associated with:

- Age^{1,2}
- Severe and/or multiple comorbidities^{1,2}
- Length of hospital stay²
- Admission to an intensive care unit^{2,3}
- Readmission within 30 and 90 days²
- 48-hour, 30-day and 90-day mortality²

This means that in **acute medical patients**, suPAR measured on admission is higher in **elderly** patients, patients who end up being **admitted for a long period**, patients ending up in the **intensive**

care unit, seriously or chronically ill patients, and multimorbid patients as well as patients who are readmitted or die within 30 as well as 90 days¹⁻⁴.

Even taking into account other well-known prognostic factors, including sex, age, Charlson score, and CRP, suPAR still remains an independent predictor of readmission and mortality within 30 as well as 90 days².

On the other hand, **patients with a low suPAR level** are at a lower risk of being readmitted or dying compared to others of the same age. Example:

- The background 30- and 90-day mortality in patients below the age of 70 is 1.5% and 2.9%, respectively.
- In a patient below the age of 70 with a suPAR level of **0-3 ng/mL**, the risk of dying within 30 and 90 days is 0.3% and 0.8%, respectively.
- By comparison, in a patient below the age of 70 with a suPAR level **above 9 ng/mL** the risk of dying within 30 and 90 days is 19.7% and 27.6%, respectively².

Diagnoses

The suPAR level is elevated in emergency medical patients with:

- cancer, diabetes, dementia, paralyses, cardiovascular diseases, chronic pulmonary diseases, peptic ulcer, hepatic diseases, rheumatic diseases, and renal/urinary tract diseases^{1,2,4}.

Data from Hvidovre Hospital emergency department².

Age: Median (25-75%) suPAR level:

- 0-50 years: 2.3 ng/mL (1.8-3.0)
- 50-70 years: 3.0 ng/mL (2.3-4.2)
- >70 years: 4.4 ng/mL (3.2-6.1)

Length of hospital stay: Median suPAR level (25-75%):

- 0 days: 2.6 ng/mL (1.9-3.6)
- 2-4 days: 3.7 ng/mL (2.7-5.3)
- >10 days: 5.1 ng/mL (3.6-7.5)

Admission to intensive care unit:

Median suPAR level (25-75%):

- ÷ intensive care unit: 3.2 ng/mL (2.2-4.6)
- + intensive care unit: 5.6 ng/mL (3.0-7.9)

Charlson score (number and severity of comorbidities):

Median suPAR level (25-75%):

- No comorbidities: 2.9 ng/mL (2.1-4.2)
- Charlson score = 1: 3.7 ng/mL (2.7-5.4)
- Charlson score \geq 4: 7.2 ng/mL (4.8-10.9)

Readmission: Median suPAR level (25-75%):

- Neither readmission nor mortality within 30 days: 3.0 ng/mL (2.2-4.2)
- Readmission within 30 days: 3.9 ng/mL (2.7-5.6)

Mortality (see Appendix 1):

Median suPAR level (25-75%):

- Survived for 30 days: 3.1 ng/mL (2.2-4.5)
- Died within 30 days: 6.8 ng/mL (4.7-9.9)
- 30-day mortality AUC: 0.84 (95% CI: 0.81-0.86)

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suPAR in infectious diseases

The suPAR level is elevated in patients with infectious diseases compared with healthy individuals, and an elevated level is associated with:

- Advanced disease
- Poor prognosis

This applies to various infectious diseases, among others:

- HIV¹⁻³
 - Sepsis⁵⁻¹¹
 - Hepatitis B¹²
 - Hepatitis C¹³⁻¹⁴
 - Tuberculosis¹⁵⁻¹⁷
 - Malaria¹⁸⁻¹⁹
 - Meningitis²¹⁻²²
 - Pneumonia²⁴⁻²⁵
-

In general, the suPAR level is slightly elevated **in patients with infectious diseases**, and in all infectious diseases studied, an elevated suPAR level is associated with a poorer prognosis. In infectious diseases, the diagnostic value of suPAR is weak, but instead it has a prognostic value.

In patients with **HIV infection**, it was demonstrated that the suPAR level is slightly elevated and increases with the disease stage (WHO criteria). The first study of suPAR in HIV showed that suPAR was at least as strong a prognostic marker of the natural progression of HIV as CD4 and viral load¹. Antiretroviral therapy (ART) causes a decrease in suPAR of about 17%². However, after 5 years of treatment, the patients' suPAR level is still higher than in healthy controls². Side effects of treatment are associated with higher suPAR

levels³. In addition to the correlation with virological and immunological effects of the infection, the suPAR level correlates with age, metabolic syndrome, smoking, and low muscle mass⁴.

In patients with **sepsis**⁵⁻⁷, it has been found that the suPAR level is of some diagnostic value, as it increases with seriousness of sepsis and is frequently above 10 ng/mL in patients with impaired organ function^{8,9}. However, most studies show that CRP and procalcitonin (PCT) are better diagnostic markers of bacterial sepsis, whereas suPAR is the best prognostic marker^{6,10}. In a later cohort it was shown and validated that suPAR in combination with the APACHE score can improve the risk stratification of patients with sepsis¹¹.

The suPAR level is elevated in **hepatitis B patients** with hepatic fibrosis compared to patients with no or mild fibrosis. Thus, suPAR may be useful for identification of hepatitis B patients with significant fibrosis¹².

In **hepatitis C patients** the suPAR level is elevated, and the level increases with the severity of fibrosis. Because hepatic disease and fibrosis affect the suPAR level, the prognostic value and the reflection of disease severity are probably a result of the liver condition rather than the hepatitis C infection¹³. This is supported by data demonstrating that suPAR is also associated with seriousness and prognosis in patients with non-alcoholic fatty liver disease¹⁴.

Active tuberculosis (TB) causes a substantial increase in suPAR level, typically to about 6-7 ng/mL – the higher, the worse^{15,16}. A study from Guinea-Bissau has shown that the suPAR level measured upon initiation of treatment for TB is a prognostic marker of mortality during treatment. Measurement of suPAR following one month of treatment demonstrated that the change in suPAR level was also associated with mortality; patients experiencing no decrease – or even an increase – in suPAR level have a poorer

prognosis than patients experiencing a decrease following one month of treatment¹⁷.

In **malaria**, suPAR has been studied in children, adults, and pregnant women. In children, a doubling of the suPAR level is observed, which decreases back to a normal level following 14 days of effective treatment¹⁸. In adult patients with malaria and acute renal damage, suPAR was associated with severity of the renal damage and was higher in patients who subsequently needed dialysis¹⁹. In pregnant women infected with malaria, a high suPAR level is associated with low birth weight of the baby²⁰.

An elevated suPAR level in the cerebrospinal fluid (CSF) in children and adults with **meningitis** is associated with increased mortality^{21,22}.

In children with **pneumonia**, suPAR is associated with the severity of the infection and length of hospital stay²³. In adults with sepsis and ventilator-associated pneumonia, the suPAR level is strongly and independently associated with a negative prognosis²⁴.

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suPAR in cancer

The suPAR level is elevated in cancer patients compared to healthy individuals, and a high suPAR level is associated with:

- Advanced disease
- High TNM stage
- Aggressive and invasive tumor growth
- Metastatic disease
- Poor prognosis

This applies to various types of cancer, among others:

- Acute leukemia¹
- Colorectal cancer²⁻⁴
- Hepatic cancer⁵
- Cervical cancer⁶
- Lung cancer (small cell and non-small cell)⁷
- Lymphomas⁸
- Ovarian cancer⁹
- Pancreatic cancer¹⁰
- Prostate cancer¹¹
- Esophageal cancer³
- Gastric cancer^{3,12}

Thus, various cancers cause an elevated plasma suPAR level. The more serious and advanced disease, the higher suPAR level. suPAR is therefore also a prognostic marker in cancer patients reflecting mortality. Cancer patients with a low suPAR level have a better chance of progression-free survival.

In the general population, an elevated suPAR level is associated with an increased risk of lung cancer and other cancers. Among

smokers, the risk of lung cancer is also higher in individuals with an elevated suPAR level compared to those with lower suPAR levels¹³.

In **prostate cancer** patients, the suPAR level is higher than in patients with benign prostatic hyperplasia¹¹.

In **neurologic patients** with paraneoplastic cerebellar syndromes or carcinomatous meningitis, the suPAR level is also elevated in plasma and in cerebrospinal fluid¹⁴.

In patients with **gastrointestinal cancers**, the suPAR level is higher in patients with esophageal cancer than in patients with colorectal cancer³.

suPAR in relation to cancer diagnostics and other biomarkers

In **patients with liver diseases**, an elevated suPAR level has proved to be an early predictor of future development of hepatocellular carcinoma, and the suPAR level may be elevated as early as 1-7 years prior to appearance of imaging signs of hepatic cancer. In this study, suPAR was statistically stronger than alpha-fetoprotein⁵.

In patients with **ovarian tumors**, a combination of suPAR and CA-125 is able to discriminate benign tumors from malignant tumors (AUC 0.94; 95% CI 0.90-0.98)⁹.

suPAR in cancer treatment

In patients in with resectable **colorectal cancer**, the suPAR level is lower than in patients with unresectable disease receiving palliative treatment^{3,4}.

In women with **cervical cancer**, the suPAR level decreases significantly following surgery⁶.

In patients with **acute leukemia**, the suPAR plasma level correlates with the number of circulating tumor cells, and following treatment with chemotherapy, the suPAR level decreases to a normal level in parallel with a reduction in the number of tumor cells¹.

Thus, a high suPAR level in cancer patients is associated with a poor prognosis and a shorter survival^{4,10–12}.

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suPAR in endocrinology

The suPAR level is elevated in patients with inflammation, cancer, and chronic diseases and is associated with:

- Incidence of type 2 diabetes^{1,2}
 - Incidence and duration of type 1 diabetes³
 - Type 1 diabetes complications³
 - Obesity²
-

In a Danish cohort of healthy individuals significantly higher suPAR values were found in those, who developed **type 2 diabetes**. In the group of middle-aged non-smokers, the risk of developing diabetes was significantly higher in individuals with a high suPAR level compared to those with a low suPAR level. The increased risk remained following adjustment for fasting blood glucose, age, sex, and insulin levels. A similar risk was found in the elderly¹.

Similarly, among **overweight** individuals (BMI 25-30) with impaired glucose tolerance and a high suPAR level an increased risk of developing diabetes is observed².

In **type 1 diabetics** with an eGFR >15 mL/min/1.73 m², the suPAR level is significantly higher than in healthy controls (3.5 vs. 2.3 ng/mL), and the suPAR level is associated with duration of the diabetes. Moreover, the suPAR level is independently associated with **diabetes complications**. Thus, the median suPAR values in normoalbuminemia and macroalbuminemia are 3.0 ng/mL and 4.9 ng/mL, respectively. For each additional diabetes complication there is a stepwise increase in suPAR level: Number of complications: 0-4: 2.6 ng/mL (1.1-6.2); 3.0 ng/mL (1.6-10.5); 3.8 ng/mL (1.9-10.3); 4.3 ng/mL (2.1-15.1) and 4.9 ng/mL (2.9-13.2), respectively, p<0.001³.

Moreover, in diabetic patients with a high suPAR level the risk of **cardiovascular diseases, autonomic dysfunction, and albuminuria** is significantly higher than in patients with a low suPAR level³.

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suPAR in neurology

The suPAR level is associated with:

- Atherosclerosis^{1,2}
 - Carotid plaques³
 - Cardiovascular diseases and diabetes^{4,5}
 - Cerebrovascular diseases^{6,7}
 - Ischemic stroke⁷
-

The uPA/uPAR system plays a key role in the pathogenesis of atherosclerosis and vascular diseases^{1,2}. In addition to the role in fibrinolysis and activation of plasminogen into active plasmin, an elevated suPAR level has been found in relation to **carotid plaques**, and the occurrence of uPAR is increased in atherosclerotic lesions³.

An elevated suPAR level is found in patients with symptoms of **cerebrovascular diseases** like **amaurosis fugax**, **transient cerebral ischemia (TCI)**, and **stroke**⁶.

In patients with carotid plaques, the suPAR level is significantly higher compared to patients with no plaques. After adjustment for risk factors, it was found that patients with a high suPAR level (median 3.7 ng/mL) and carotid plaques are at a significantly higher risk of experiencing an **ischemic stroke** compared to patients with a low suPAR level (median 2.3 ng/mL) and no plaques⁷.

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suPAR in cardiovascular diseases

The suPAR level is elevated in patients with cardiovascular diseases compared to healthy individuals, and the suPAR level is associated with:

- Atherosclerosis¹
- Ischemic heart disease^{2,13,21}
- Poor prognosis^{2,16,18,19}
- Venous thromboembolism²⁰

As well as incidence of:

- Cardiovascular diseases in the general population⁷⁻¹¹
-

suPAR is a promising biomarker of cardiovascular diseases, as it reflects “low-grade inflammation” and is associated with lifestyle factors like smoking, alcohol, and an inactive lifestyle. Previous studies have shown, that the **uPA/uPAR-system** plays a key role in the **pathogenesis of atherosclerosis**¹. Physiologically the system is involved in **fibrinolysis**, **angiogenesis**, and **immune function**, including leucocyte migration, proliferation, and degradation of matrix during tissue remodeling in the atherosclerotic plaque². uPAR is expressed in various cells involved in the development of atherosclerosis, including macrophages, endothelial cells, and smooth muscle cells, and an accumulation of uPAR in the atheroma has been found³. uPAR plays a role in **the coagulation cascade** during plasminogen activation and fibrinolysis⁴. So far, no causal relationship between the urokinase system and atherosclerosis or cardiovascular diseases has been shown². However, new data have demonstrated an association between suPAR and focal segmental glomerulosclerosis. The kidneys play a key role in blood pressure and fluid balance regulation, and therefore suPAR may be associated with heart failure and myocardial strain^{5,6}. A similar

suPAR-mediated effect on endothelial cells and platelets may potentially play a role in vascular inflammation and thrombosis⁵.

In five large studies, including a total of 4866 individuals⁷⁻¹¹, suPAR is a predictor of **cardiovascular morbidity and mortality in the general population** even after adjustment for the well-validated Framingham risk score¹¹ and taking into account well-known risk factors, CRP, and other biomarkers associated with cardiovascular diseases. In general, the prognostic value of baseline suPAR level appears to be strongest in the younger age groups and in males¹¹.

In patients with **ST-segment elevation myocardial infarction (STEMI)** treated with primary PCI, the suPAR level is elevated the first 24 hours after admission. Following adjustment for traditional risk factors, age, sex, CRP, creatinine, troponin T, total cholesterol, diabetes, and hypertension, suPAR remains associated with mortality and a **new myocardial infarction**². In non-survivors, baseline suPAR values are significantly higher than in survivors (4.9 ng/mL vs. 3.9 ng/mL), and all-cause mortality increases significantly with higher suPAR values².

Following adjustment for sex and age, suPAR was associated with an increased risk of developing **atrial fibrillation**. However, this association disappeared following adjustment for well-known risk factors⁶.

In **uremic patients** receiving peritoneal dialysis or hemodialysis, the suPAR level and the carotid intima-media thickness (IMT) in the two dialysis groups are significantly higher than in healthy age- and sex-matched controls, and in a smaller study, suPAR is associated with IMT¹².

suPAR is also a prognostic marker of **cardiovascular diseases in patients with mild to moderate chronic renal diseases**, including cardiac mortality, non-fatal MI, myocardial ischemia, coronary intervention, ischemic stroke, and newly diagnosed peripheral

vascular diseases¹³. suPAR and eGFR are comparable in estimating mortality risk, and in this population suPAR was a stronger cardiovascular risk predictor than eGFR¹³.

In patients admitted with suspected **acute coronary syndrome (ACS)**, suPAR is a strong predictor of mortality and of readmission due to heart failure and a **new myocardial infarction**. Thus, in non-survivors, the baseline suPAR level was significantly higher than in survivors, and, similarly, the suPAR level was higher in readmitted patients than in non-readmitted patients. The study concluded that in patients with suspected ACS, suPAR improves risk stratification beyond traditional risk factors¹⁶.

In a South African study, the baseline suPAR level was not able to predict development of **hypertension**, but on the other hand, a change in suPAR level was to some extent associated with increasing blood pressure during the observation period¹⁷.

In patients resuscitated from a **cardiac arrest** and treated with hypothermia, suPAR was studied as a potential prognostic tool. One study found that the suPAR level 6 hours after the cardiac arrest was strongly associated with mortality and neurological outcome¹⁸. Similarly, in another study, suPAR was strongly associated with mortality but not with neurological outcome¹⁹. In patients with non-shockable rhythms, the baseline suPAR level was significantly higher than in patients with shockable rhythms¹⁹.

High suPAR levels are associated with incidence of **venous thromboembolism**²⁰. No significant association between pulmonary embolism and suPAR was found²⁰.

In males and females with **carotid plaques**, the suPAR level is significantly higher than in individuals with no carotid plaques^{21,10}. Similarly, suPAR is a predictor of **ischemic heart disease (IHD)**,

and in patients with both elevated suPAR level and carotid plaques, the risk of developing IHD is significantly increased²¹.

Following adjustment for traditional risk factors and subclinical organ damage, suPAR remains associated with **cardiovascular mortality**¹⁰.

Furthermore, in a study of 1126 Danes it was shown that suPAR is able to predict **coronary artery calcifications** in healthy individuals, as assessed by cardiac CT scan, and that suPAR is associated with calcium score⁸.

Surgical stress related to **coronary bypass** does not induce significant changes in suPAR level 6 or 24 hours postoperatively compared to the preoperative value²³.

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suPAR in pulmonary diseases

The suPAR level is elevated in patients with infections and chronic diseases of the lungs and respiratory tract compared to healthy individuals, and a high suPAR level is associated with:

- Bacteremia and sepsis¹⁻⁴
 - Pneumonia⁵⁻⁷
 - Asthma and poor disease control in asthma⁸
 - COPD and in relation to an exacerbation^{9,10}
 - Incidence of future respiratory cancer¹¹
 - Poor prognosis¹⁻⁷
-

In general, the suPAR level reflects immune activation regardless of etiology, and therefore the suPAR level is of no diagnostic value. However, in **SIRS** patients it has been demonstrated that the suPAR level is able to discriminate patients with **bacteremia** from patients with no bacteremia. A combined model using suPAR, procalcitonin, and IL-6 showed an AUC of 0.804 for prediction of bacteremia in SIRS patients¹.

The **prognostic** value of suPAR has been studied among patients with *S. pneumoniae* **bacteremia**² and in patients with *S. pneumoniae*, *S. aureus* or *E. coli* bacteremia³. In both situations, significantly higher suPAR values were found in non-survivors. In the bacteremia patients, a sensitivity of 83% and a specificity of 76% for mortality is found using a cut-off value of 11.0 ng/mL. A similar prognostic value is found in a study of patients with sepsis. Here, a cut-off value of 12 ng/mL is linked to a >80% sensitivity and a negative predictive value of 94.5% for mortality⁴. In mechanically ventilated **patients**⁵ and in **children with pneumonia**^{6,7}, the suPAR level is elevated and associated with seriousness of the disease and a poorer prognosis.

The suPAR level correlates with respiratory obstruction and can potentially help with the objective assessment of **asthma**⁸. In addition, the median suPAR level is significantly higher in asthmatics compared to healthy individuals (3.3 ng/mL vs. 2.5 ng/mL)⁹.

Similarly, in **COPD patients**, the suPAR level is significantly higher compared to healthy individuals, and the median level is above the level in asthma patients (5.8 ng/mL vs. 3.3 ng/mL)⁹.

Serum suPAR, CRP, and fibrinogen are significantly higher in **COPD patients experiencing an exacerbation** compared to healthy controls (4.8 ± 1.9 ng/mL vs. 2.4 ± 0.9 ng/mL, respectively). suPAR was superior to fibrinogen and CRP in identifying COPD patients experiencing an exacerbation, and in multivariable analyses, only suPAR and fibrinogen were predictors of an exacerbation. Moreover, a negative correlation between suPAR and lung function, measured by **FEV1**, was found⁹.

In the general population, suPAR is associated with the incidence of **respiratory cancer**, even after adjustment for traditional risk factors, CRP, and leucocytes¹⁰.

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suPAR in gastroenterology

The following factors are associated with an **elevated** suPAR level:

- Cirrhosis^{1,2,5}
- Alcoholic liver disease³
- Excessive alcohol consumption³
- Hepatic fibrosis⁴
- Acute liver failure⁶
- Alcoholic pancreatitis⁷
- Poor prognosis^{1-5,7}

In addition, an elevated suPAR level is associated with **future** incidence of:

- Hepatocellular carcinoma⁸
-

Inflammation plays a key role in the development of chronic hepatic diseases, and as suPAR is a marker of the degree of inflammation, the diagnostic and prognostic value of suPAR in hepatic diseases has been studied.

The suPAR level is significantly higher in **patients with cirrhosis** compared to healthy controls^{1,2}. In a study of 159 patients with **chronic hepatic diseases**, including 98 patients with cirrhosis, the diagnostic ability of suPAR in identifying cirrhosis was good, and suPAR was a strong predictor of mortality or need of transplantation. A cutoff level >9 ng/mL predicted a poor prognosis with a sensitivity and specificity of 70.7% and 77.8%, respectively, as well as a relative risk of 8.5 (3.5-20.3)¹.

The suPAR level is higher in patients with alcoholic etiology and correlates positively with fibrosis^{1,3,4}. In addition, the suPAR level is

higher in individuals with **excessive alcohol consumption** compared to healthy individuals³.

In patients with **decompensated cirrhosis**, the suPAR level is significantly higher (median 12.9 ng/mL) than in patients with compensated cirrhosis (8.9 ng/mL), and suPAR is associated with 28-day mortality⁵.

In patients with **spontaneous bacterial peritonitis**, an elevated suPAR level in ascites fluid was found, and the level was associated with severity and prognosis⁵.

In a small study of patients with **acute liver failure**, a high median suPAR level of 13.2 ng/mL was found. Similarly, a strong correlation between suPAR and declining liver function (increasing AST/ALT and INR), independently of the etiology, was found⁶.

A study of 104 patients shows that the suPAR level on admission was superior to CRP, hematocrit, and creatinine as a prognostic marker of the severity of **acute alcoholic pancreatitis**. Using a cut-off value of 5 ng/mL, the sensitivity and specificity for predicting moderate or serious pancreatitis were 79% and 78%, respectively. The suPAR level was significantly associated with severity: Mild and moderate/serious: 4.2 ng/mL vs. 6.2 ng/mL, respectively⁷.

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suPAR in nephrology

The suPAR level is associated with:

- Chronic renal diseases³
 - Future incidence of chronic renal diseases⁴
 - Declining eGFR^{4,5}
-

In the kidneys, suPAR plays a role in the regulation of the permeability of the glomerular filtration barrier, and suPAR may be involved in podocyte damage and development of **focal segmental glomerulosclerosis** and **diabetic nephropathy**^{1,2}.

The suPAR level increases in **patients with chronic renal diseases**, and a high level is significantly associated with mortality and incidence of cardiovascular diseases in these patients³.

The association between suPAR and chronic renal diseases has been further studied in a large study⁴. It was found that the suPAR level was an independent predictor of **declining eGFR**. During the study follow-up period of 3.7 years, the decline in eGFR in subjects in the lower suPAR quartile was 0.9 mL/min/1.73 m² and 4.2 mL/min/1.73 m² in the upper quartile.

In 1335 individuals with an eGFR >60 mL/min/1.73 m² at study start, a suPAR level in the upper quartile was associated with a significantly increased **incidence of chronic renal diseases** compared to those in the lower quartile; all in all, a 3-fold increased risk⁴.

In patients with **primary and secondary glomerulonephritis**, an elevated suPAR level is similarly associated with reduced eGFR and presence of **proteinuria**⁵.

Reduced renal function causes a significant increase in suPAR level, and in hemodialysis patients, the mean value is 14.8 ng/mL. In this group of patients, a high level is associated with increased mortality and increased risk of hospitalization⁶.

-
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suPAR in intensive care

In critically ill patients, the suPAR level is significantly increased. suPAR is an independent prognostic marker, and the change over time correlates with organ dysfunction.

suPAR is elevated and has a prognostic value in patients with:

- SIRS (systemic inflammatory response syndrome)^{1,2}
 - Sepsis/septic shock³⁻⁹
 - Burn injuries¹⁰
 - Traumatic brain injuries¹¹
-

The suPAR level reflects the body's immune response to infections, and the level increases with the **severity of the infection**. In patients with **organ dysfunction**, the suPAR value is often a two-digit value. In particular hepatic and renal dysfunction affects the suPAR level³⁻⁵.

suPAR has been studied in **patients with SIRS** who were acutely admitted to the emergency department (n=902). The studies showed that suPAR is a stronger marker of 2-day, 30-day, and 90-day mortality than age, CRP, IL-6, creatinine, and procalcitonin. However, for diagnostic purposes, IL-6 and CRP are superior to suPAR in predicting a positive blood culture^{1,2}.

A Greek multicenter study including 1914 **patients with sepsis** showed that suPAR is a strong predictor of mortality, and that a suPAR level above 12 ng/mL is linked to a >80% sensitivity for mortality and a negative predictive value of 94.5%⁶.

In addition, the prognostic value of suPAR in patients with sepsis is independent of relevant covariates like APACHE score, CRP, etc.⁶⁻⁹.

In patients with **burn injuries** and **inhalation trauma** requiring mechanical ventilation, the plasma suPAR level and BAL fluid level correlate to IL-6 and coagulation factors. An elevated plasma suPAR level is associated with prolonged ICU stay and the duration of mechanical ventilation¹⁰.

The suPAR level is elevated in patients with **traumatic brain injury**. In trauma patients who suffered a brain injury within 12 hours prior to blood sampling, the mean suPAR level is 14.9 ng/mL \pm 6.9 vs. 2.8 ng/mL \pm 0.7 in control subjects. In these patients suPAR is associated with severity of the brain injury and with mortality¹¹.

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suPAR in surgery

The suPAR level is elevated in patients with infections, chronic diseases, and cancer compared to healthy individuals. A high suPAR level is associated with:

- Increased mortality risk³
 - Poor prognosis^{5,6,8-10}
 - Postoperative pneumonia⁷
 - Prosthetic joint infection¹¹
-

suPAR is a well-studied biomarker predicting prognosis, disease severity, and organ dysfunction and is being considered as a marker of the individual's inflammatory status. It has been demonstrated that biomarkers are able to improve triage and are effective in identifying high and low risk patients among acutely admitted patients¹. Improving the preoperative risk stratification using biomarkers may optimize the patient's clinical outcome². Available data on use of biomarkers in addition to risk stratification are observational data, and suPAR has mainly been studied in medical and oncological patients.

Gastric surgery patients and orthopedic surgery patients were included in a study conducted in the emergency department at Hillerød Hospital, Denmark. The TRIAGE study included 5992 unselected patients and confirmed the prognostic value of suPAR regarding mortality, and found it similar in both medical and surgical patients.

In the same study, it was shown that triage based on suPAR level was superior to the current triage system in predicting 30-day mortality: AUC 0.84 (0.82-0.87) vs. 0.62 (0.58-0.66), respectively. In multivariate analyses of 30-day mortality in relation to suPAR

quartiles, adjusted for sex, age, CRP, leucocytes, and triage category, HR was 1.0, 2.2, 8.3, and 26.9 in the upper quartile³.

A high suPAR level has been demonstrated in both tumor tissue and in blood, and in several **cancers**, the suPAR level is shown to correlate with a poor prognosis⁴. In a few studies, suPAR has been studied as a potential biomarker in gastric surgery.

In a cohort of 518 elective **colorectal cancer patients**, preoperative measurement of the suPAR level was performed. In multivariate analyses adjusted for age, sex, tumor classification, and localization, suPAR was significantly associated with mortality, HR 1.74 (1.33-2.26; $p < 0.0001$). In addition, the suPAR level was associated with tumor stage and localization; and in **colon cancer** patients the suPAR level was significantly higher compared to **rectal cancer** patients⁵. The same cohort was also followed in another study, in which the suPAR plasma level was found to be an independent prognostic marker⁶.

To identify risk patients among elective **colon cancer patients** the suPAR level was studied. In patients receiving **blood transfusion** during surgery, the suPAR level was higher, and a significant association between the suPAR level and **postoperative infections** was shown. Occurrence of **pneumonia** was significantly associated with the suPAR level, but any significant association with other infectious complications could not be found⁷.

In patients with **gastric cancer**, the suPAR level was significantly higher compared to healthy controls ($2.3 \text{ ng/mL} \pm 0.77$), and the suPAR level was significantly higher in cancer patients with metastatic disease ($7.0 \text{ ng/mL} \pm 6.1$) than in patients with no metastases ($4.8 \text{ ng/mL} \pm 4.4$). In the group of patients with a suPAR value above 5.2 ng/mL , the mortality was significantly increased⁸.

In patients with rectal cancer⁹ and colon cancer¹⁰, a similar prognostic value is found, indicating an increased mortality risk.

suPAR in orthopedic surgery

The diagnostic value of suPAR in **prosthetic knee/hip joint infection** has been examined in a study. The study included 80 patients of which 45 experienced prosthetic joint infection defined by presence of clinical signs (swelling, redness, tenderness, and pus inside the joint) and a positive culture. In these patients, a significantly higher median suPAR level (6.8 ng/mL) was found compared to patients without infection, who had revision surgery done. Furthermore, suPAR was positively correlated with CRP, and the study showed that suPAR was more precise in diagnosing prosthetic knee/hip joint infection than CRP¹¹.

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Line Jee Hartmann Rasmussen

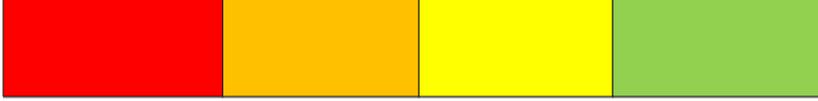
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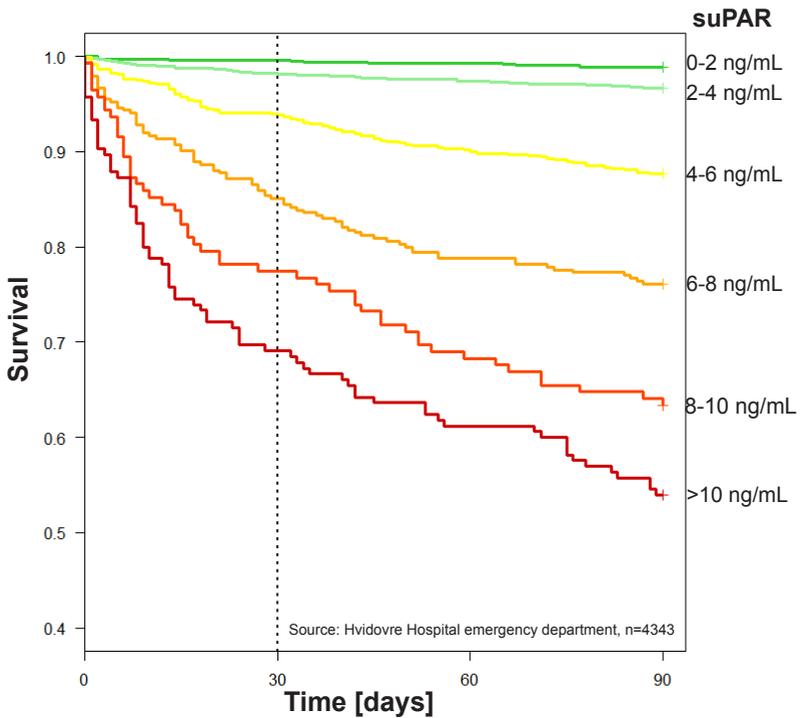
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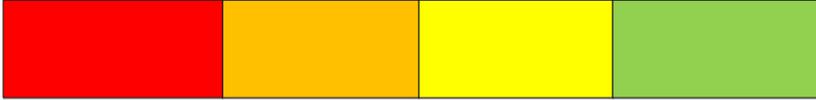
Kasper Karmark Iversen

Martin Schultz



Have you considered your patient's prognosis?





suPAR level and mortality risk

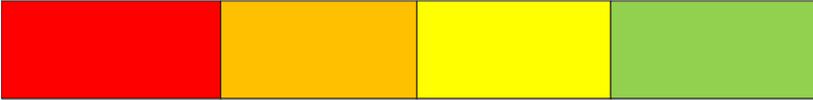
Patients below the age of 70:

suPAR (ng/mL)	30 days	90 days
All (n=5925)	1.4%	2.5%
0-3 (n=3852)	0.2%	0.5%
3-6 (n=1661)	1.7%	3.4%
6-9 (n=287)	7.3%	11.1%
>9 (n=169)	16.6%	23.1%

Patients above the age of 70:

suPAR (ng/mL)	30 days	90 days
All (n=3666)	8.8%	15.3%
0-3 (n=750)	2.3%	3.5%
3-6 (n=1970)	5.3%	10.9%
6-9 (n=567)	16.6%	28.1%
>9 (n=379)	27.7%	43.0%

Source: The emergency departments at Hvidovre Hospital and Hillerød Hospital, Denmark. n=9591.



P-[suPAR]

Soluble urokinase plasminogen activator receptor

Unit: ng/mL

Interval: 0.1-16.0

Analysis time: 20 min; the result is available in laboratory systems within 2 h.

Interpretation:

Elevated values are observed in pathological conditions and correlate with the patient's mortality risk.

- **Highly elevated** values (>9) are observed in patients with multiple chronic diseases and/or serious and life-threatening conditions like severe sepsis or seriously impaired organ function. Mortality risk is highly increased.

- **Moderately elevated** values (about 4-9) are, for example, observed in the following conditions: Infections, cancer, COPD, cardiovascular diseases, dementia, diabetes, hepatic and renal diseases. Mortality risk and readmission risk are increased.

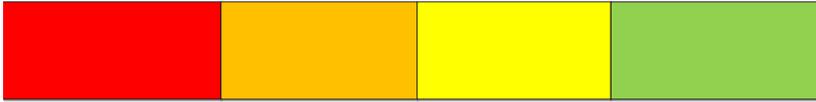
- **Low values** (<3) indicate a good prognosis.

Comments:

- The suPAR level should be considered in relation to medical history, clinical findings, and other paraclinical findings.

- If the suPAR level is elevated for no obvious reason, further investigation for an unacknowledged disease may be considered.

- A low suPAR level indicates a low mortality risk and a low risk of critical illness and may support a decision to discharge the patient.



How sick is your patient?

suPAR level

12+	HIGH RISK Significantly increased mortality risk Critical illness, organ failure Severe sepsis, septic shock Multiple chronic diseases
9	
6	MODERATE RISK Increased mortality risk Prolonged hospital stays Increased readmission risk Infections and acute illness Chronic diseases, e.g. COPD, diabetes, cardiovascular diseases, dementia, peptic ulcer, cancer, hepatic diseases, renal diseases
3	
0	LOW RISK Low mortality risk Low readmission risk No or well-treated comorbidities Healthy individuals

suPAR Monograph version 1 – February 2016