[suPAR]

Monograph

Content:

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 individual[1]. 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 population[2-15]. 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 as 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 chemotaxis[1].

The suPAR protein was discovered in 1992[1]. Since its discovery, it has become evident that suPAR is elevated in patients with disease[12] (including cardiovascular, hepatic, renal, and pulmonary diseases), and various infectious diseases[17-22] (tuberculosis, HIV, malaria, sepsis, meningitis, pneumonia). Furthermore, and most importantly, the higher the suPAR level, the worse the prognosis. 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[2,16].

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 fluid[23]. 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.

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 smoking[1–5]
- Obesity[3]
- Previous AMI[3]
- Low HDL cholesterol/high LDL cholesterol[1–3]
- Unhealthy diet[3, 10]
- Physical inactivity[3]
- Age[1–3,5,6]

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

- Mortality[1]
- Cardiovascular diseases[1,2,8]
- Cancer[1,5]
- Type 2 diabetes[1]
- Renal failure[7]

Finally, a change towards a healthier lifestyle is associated with a suPAR decrease – and the resultant suPAR is predictive of outcome (mortality). Hence, suPAR is not a death sentence – it is an early warning signal[8]

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[1–5,7,8].

Moreover, an **unhealthy diet**[3,9] and, to a lesser extent, **physical inactivity** may also increase the suPAR level[3]. 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 levels[9]

Cardiovascular risk factors affect the suPAR level, as there is a slightly positive association with LDL-cholesterol and a clearly negative association with HDL-cholesterol[1–3]. **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 confirmed[3]. A BMI of 20-35 kg/m^2 has no notable effect on the suPAR level, but in **severe obesity** (BMI > 40) the suPAR level is about 0.5 ng/mL higher than in normal weight individuals[3].

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].

Excitingly, data from the Danish Inter99 cohort[8] 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[8].

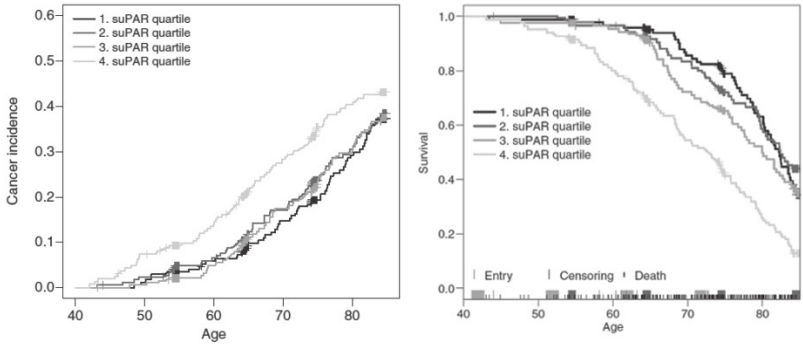

Figure 1. ***The left graph*** *displays cancer incidence during a 12.6-year follow-up of 2,602 individuals in the Danish MONICA cohort. The suPAR level is below 3.4 ng/mL in the 1st quartile and above 4.9 ng/mL in the 4th quartile.* ***The right graph*** *displays mortality in the 1,310 males in the 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/mL[3]. This exceeds the difference between the 1st and 4th suPAR quartile in Figure 1 and therefore indicates a considerable risk difference.

A change towards healthier lifestyle reduce suPAR and the resultant suPAR predict mortality.

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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 stay[2]
- Admission to an intensive care unit[2,3]
- Readmission within 30 and 90 days[2]
- 48-hour, 30-day and 90-day mortality[2]

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 days[1–4].

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 days[2].

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[2]
- 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[2]
- 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%, respectively[2].

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 department[2].

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 ≥ 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)

suPAR and clinical signs

suPAR is correlated with disease severity, but is suPAR correlated to the clinical signs? In a study published in Critical Care Medicine in 2018, the authors found that suPAR is correlated to the number of clinical signs (registered using the NEWS score) – however, many patients with none or 1 clinical sign had high suPAR (Figure 2) and these patients (as illustrated with the red box) had high risk of mortality[5]. Interestingly, suPAR was even stronger for those with none or few clinical signs compared to those presenting with multiple clinical signs, perhaps because these patients do not receive the same level of clinical attention[5].

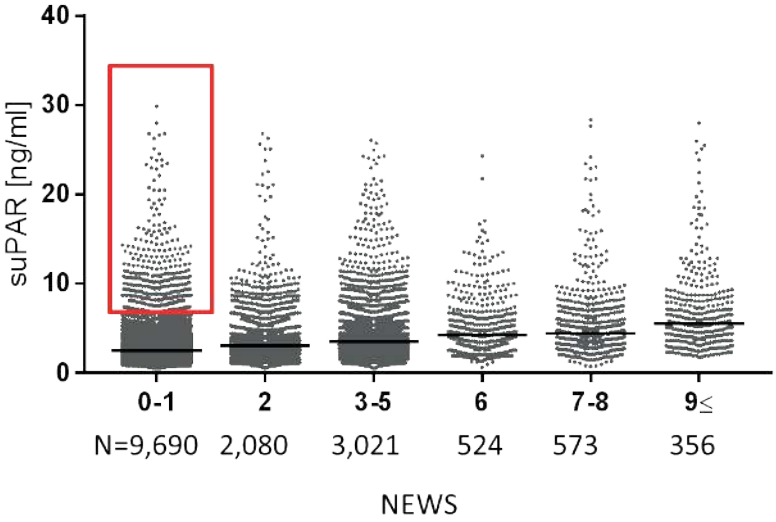

Figure 2: suPAR levels according to NEWS score. N denotes the number of acute medical patients in each group. The red box illustrates that patients with 0-1 in NEWS score can have a high suPAR level[5].

suPAR in a randomized controlled trial

An RCT including more than 16.000 acute medical patients showed that patients who had the **suPAR level measured** (suPAR group) were **significantly more often discharged** within 24 hours of admittance compared to patients without suPAR levels measured (control group). Furthermore, the **mean length of hospital stay** in the suPAR group was **6,5 hours shorter** compared to control group ($p<0.05$).[6]

Although significantly more patients were discharged within 24 hours, there was **no increased mortality** among these patients. In those who were discharged with suPAR, 30-day mortality was 1,3% and in the control arm it was 1,8% ($p=0.08$). The suPAR AUC for 30-day mortality among the patients discharged within 24 hours was 0.92.[7] Further analysis of the triage data showed that the Youden index was 5,9 ng/ml. Triaging patients down with suPAR below and up above the Youden index (5,9 ng/ml) resulted in 34% more patients triaged green (Figure 3).

Included N=4420	Standard triaging (%)	Triaging with suPAR (%)
Red category	251 (4.9)	369 (9.0)
Orange category	**1241 (28.5)**	**445 (10.1)**
Yellow category	1243 (28.1)	1267 (28.7)
Green category	1721 (38.9)	**2312 (52.3)**

Figure 3. Comparison on distribution of patients in triage groups between standard triage and triage with knowledge of suPAR. From Schultz et al, 2019.[7]

Clinical guidelines and cutoff values have been developed at Copenhagen University Hospital, Hvidovre in Denmark, where suPAR measurement was implemented as a clinical routine procedure in 2013 (Figure 4).

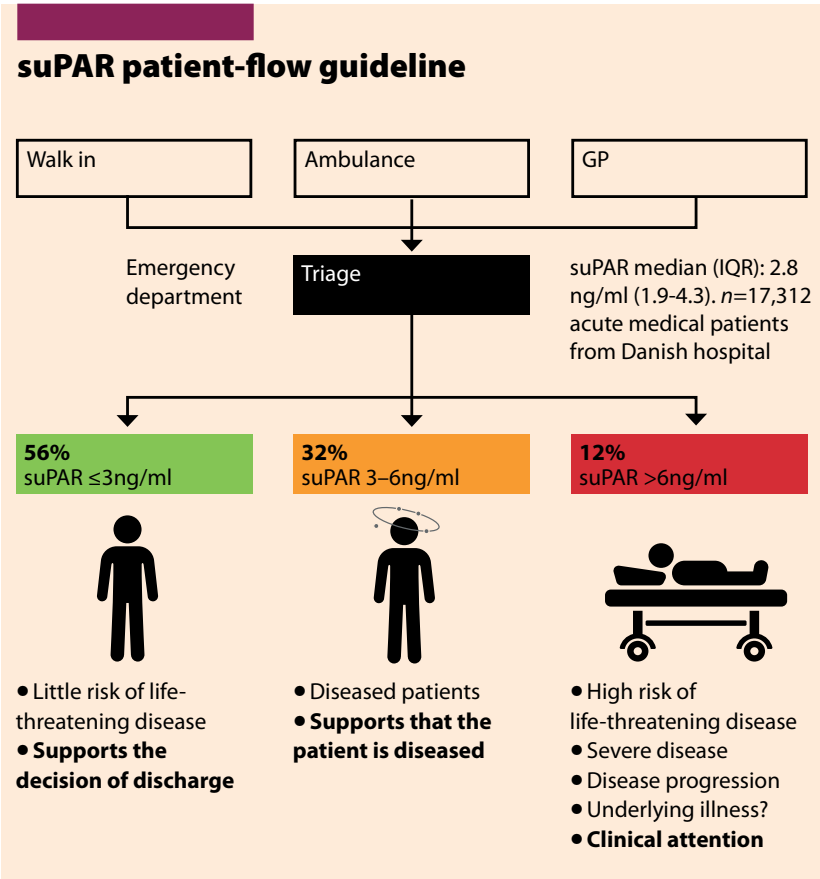

Figure 4: Guideline used at Copenhagen University Hospital Hvidovre, Denmark.

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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:

- HIV[1-5, 25]
- Sepsis[6-11]
- Hepatitis B[12]
- Hepatitis C[13-14]
- Tuberculosis[15-17]
- Malaria[18-19]
- Meningitis[21-22]
- Pneumonia[23-24]

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 load[1]. 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 controls[2]. Side effects of treatment are associated with higher suPAR

levels[3]. 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 mass[4]. In HIV patients with ART-induced viral suppression, suPAR is a superior and independent predictor of non-AIDS events comorbidities (e.g. cardiovascular and renal diseases).

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 sepsis[11].

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 fibrosis[12].

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 infection[13]. This is supported by data demonstrating that suPAR is also associated with seriousness and prognosis in patients with non-alcoholic fatty liver disease[14].

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 treatment[17].

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 treatment[18]. 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 dialysis[19]. In pregnant women infected with malaria, a high suPAR level is associated with low birth weight of the baby[20].

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 stay[23]. In adults with sepsis and ventilator-associated pneumonia, the suPAR level is strongly and independently associated with a negative prognosis[24].

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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 leukemia[1]
- Colorectal cancer[2–4]
- Hepatic cancer[5]
- Cervical cancer[6]
- Lung cancer (small cell and non-small cell)[7]
- Lymphomas[8]
- Ovarian cancer[9]
- Pancreatic cancer[10]
- Prostate cancer[11]
- Esophageal cancer[3]
- 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 levels[13].

In **prostate cancer** patients, the suPAR level is higher than in patients with benign prostatic hyperplasia[11].

In **neurologic patients** with paraneoplastic cerebellar syndromes or carcinomatous meningitis, the suPAR level is also elevated in plasma and in cerebrospinal fluid[14].

In patients with **gastrointestinal cancers**, the suPAR level is higher in patients with esophageal cancer than in patients with colorectal cancer[3].

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-fetoprotein[5].

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]. Furthermore, suPAR might help to guide preoperative treatment decisions regarding patients' outcome and to identify patients particularly susceptible to acute kidney injury[16].

In women with **cervical cancer**, the suPAR level decreases significantly following surgery[6].

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 cells[1].

In patients without known cancer but with serious nonspecific symptoms and signs of cancer referred to a diagnostic outpatient clinic for an accelerated cancer diagnostic program, elevated suPAR levels were significantly associated with newly diagnosed cancer during follow-up[15]. Thus, a high suPAR level is associated with increased risk of finding cancer patients[15]. In cancer patients, elevated suPAR levels are 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 individuals that later develop type 2 diabetes, suPAR is elevated in type 1 diabetes and strongly associated with the development of diabetes complications

- Incidence of type 2 diabetes[1,2]
- Incidence and duration of type 1 diabetes[3]
- Type 1 diabetes complications[3-4]

In a Danish cohort of healthy individuals significantly higher suPAR values were found in those, who developed **type 2 diabetes**[1]. 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 elderly[1].

Similarly, among **overweight** individuals (BMI 25-30) with impaired glucose tolerance and a high suPAR level an increased risk of developing diabetes is observed[2].

In **type 1 diabetics**, suPAR is strongly associated with development of **diabetes complications**. In a study published in Diabetes Care (2019), 36 out of 37 patients that developed end-stage renal disease within the 6-year follow-up period were in the highest suPAR quartile. Patients in the two lowest suPAR quartiles seemed to be protected against developing renal complications[3]. A low suPAR level was also protective against decline in eGFR ≥30%, cardiovascular disease and mortality[3,4].

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suPAR in neurology

The suPAR level is associated with:

- Depression[1]
- Schizophrenia[2]
- Traumatic brain injury[3]
- Adverse childhood experiences[4]

In recent years, it has become evident that there is a biological link between chronic inflammation and psychological disorders. As suPAR is a stable marker of chronic inflammation, there has been a number of papers investigating suPAR as a marker of psychological disorders.

In a Danish study including 9305 blood donors with 5-years follow-up, there was a significant association between suPAR and getting medication against **depression**. For men, the risk of first use of antidepressants increased by 72% from the 1st to the 4th quartile (HR = 1.72, 95% CI: 1.11-2.69). For women, it increased by 108% from the 1st to the 4th quartile (HR = 2.08, 95% CI: 1.45-2.98)[1].

Elevated suPAR was also observed in a Swedish study of **depressed patients** (n = 19) and **suicide attempters** (n = 54), compared to healthy controls (n = 19). Both the depressed patients and suicide attempters had increased plasma suPAR. The levels of suPAR discriminated better between controls and suicide attempters than CRP did[2].

A prospective observational study aimed to explore the relationship between the suPAR plasma concentration and **traumatic brain injury** (TBI)[3]. The study showed that the suPAR levels were strongly associated with the severity of TBI patients. The suPAR levels increased in association with the severity of brain injury, significance

being found among all three groups: severe, moderate and mild TBI. The suPAR levels in non-survivals were significantly increased compared to the survivals ($P < 0.05$). Thus, the authors conclude that the prognosis was worse in the patients with elevated suPAR levels[3].

Finally, a study of childhood risk factors and the suPAR level at age 38 was carried out in the Dunedin study[4]. After controlling for sex, body mass index (BMI), and smoking, children who experienced more **adverse childhood experiences**, had lower IQ, or had poorer self-control showed elevated adult suPAR levels. The authors conclude that exposure to more childhood risk factors was associated with higher suPAR levels, independent of CRP and that suPAR is a useful addition to studies connecting childhood risk to adult inflammatory burden[4].

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suPAR in cardiovascular diseases

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

- Atherosclerosis[1]
- Ischemic heart disease[2,13,21]
- Poor prognosis[2,16,18,19]
- Venous thromboembolism[20]

As well as incidence of:

- Cardiovascular diseases in the general population[7-11]

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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 plaque[2]. 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 found[3]. uPAR plays a role in **the coagulation cascade** during plasminogen activation and fibrinolysis[4]. So far, no causal relationship between the urokinase system and atherosclerosis or cardiovascular diseases has been shown[2]. 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 thrombosis[5].

In five large studies, including a total of 4866 individuals[7-11], suPAR is a predictor of **cardiovascular morbidity and mortality in the general population** even after adjustment for the well-validated Framingham risk score[11], 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 males[11].

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 values[2].

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 factors[6].

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 also associated with IMT[12].

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 diseases[13]. suPAR and eGFR are comparable in estimating mortality risk, however, in this population suPAR was a stronger cardiovascular risk predictor than eGFR[13].

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 factors[16].

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 period[17].

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 outcome[18]. Similarly, in another study, suPAR was strongly associated with mortality but not with neurological outcome[19]. In patients with non-shockable rhythms, the baseline suPAR level was significantly higher than in patients with shockable rhythms[19].

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

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 increased[21].

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 score[8].

Surgical stress related to **coronary bypass** does not induce significant changes in the suPAR level 6 or 24 hours postoperatively compared to the preoperative value[23].

Finally, suPAR levels were determined in 1314 patients presenting to the emergency department with suspected AMI. Patients were followed up for 12 months to assess all-cause mortality. suPAR levels reliably predicted all-cause mortality after 1 year. Hazard ratio for 1-year mortality was 12.6 ($p < 0.001$) in the highest suPAR quartile compared to the lowest suPAR quartile[24]. The prognostic value for 6-months mortality was comparable to an established risk prediction model, the Global Registry of Acute Coronary Events (GRACE) score, with an AUC of 0.79 (95% CI 0.72-0.86) for the GRACE score and 0.77 (95% CI 0.69-0.84) for suPAR. Addition of suPAR improved the GRACE score, as shown by integrated discrimination improvement statistics of 0.036 ($p = 0.03$), suggesting a **further discrimination of events from non-events by the addition of suPAR**[24]

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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 sepsis[1-4]
- Pneumonia[5-7]
- Asthma and poor disease control in asthma[8]
- COPD and in relation to an exacerbation[9,10]
- Incidence of future respiratory cancer[11]
- Poor prognosis[1-7]

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 patients[1].

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* bacteremia[3]. 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 mortality[4]. 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 found[10].

In the general population, suPAR is associated with the incidence of **respiratory cancer**, even after adjustment for traditional risk factors, CRP, and leucocytes[11].

In a study including 2838 acutely admitted medical patients with COPD as primary (AECOPD) or secondary diagnose, median suPAR levels were significantly higher among patients who died within 30 days compared with those who survived (5.7 ng/ml (IQR 3.8-8.1) vs. 3.6 ng/ml (2.7-5.1), $P < 0.0001$)[12].

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suPAR in gastroenterology

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

- Cirrhosis[1,2,5]
- Alcoholic liver disease[3]
- Excessive alcohol consumption[3]
- Nonalcoholic fatty liver disease [4]
- Acute liver failure[6, 8]
- Alcoholic pancreatitis[7]
- Poor prognosis[1-5,7]

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

- Hepatocellular carcinoma[8]

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 individuals[3].

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 mortality[5].

In patients with **spontaneous bacterial peritonitis**, an elevated suPAR level in ascites fluid was found, and the level was associated with severity and prognosis[5].

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 found[6].

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, respectively[7].

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suPAR in nephrology

The suPAR level is associated with:

- Chronic renal diseases[3]
- Future incidence of chronic renal diseases[4]
- 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 patients[3].

The association between suPAR and chronic renal diseases has been further studied in a large study[4]. 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 m^2 and 4.2 mL/min/1.73 m^2 in the upper quartile.

In 1335 individuals with an eGFR >60 mL/min/1.73 m^2 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 risk[4].

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 hospitalization[6].

Another resent study further supports the strong link between suPAR and development of kidney disease. This study of patients with type 1 diabetes showed that elevated suPAR is associated with increased risk of fast eGFR decline and of end-stage renal disease[7].

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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 shock[3-9]
- Burn injuries[10]
- Traumatic brain injuries[11]

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 level[3-5].

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 ventilation[10].

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 ± 6.9 vs. 2.8 ng/mL ± 0.7 in control subjects. In these patients suPAR is associated with severity of the brain injury and with mortality[11].

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suPAR in surgery

A high preoperative suPAR level is associated with:

- Post-operative complications
- Increased mortality risk[3]
- Poor prognosis[5,6,8-10]
- Postoperative pneumonia[7]
- Prosthetic joint infection[11]

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 patients[1]. Improving the preoperative risk stratification using biomarkers may optimize the patient's clinical outcome[2]. 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 quartile[3]. Of the acute medical patients, 697 had a surgical intervention registered within 3 months after admission. During 90-day follow-up from surgery, 31 (7.0%) patients

died and 158 (35.6%) patients had postoperative complications. After adjusting for age, sex, and ASA classification, the HR for 90-day postoperative mortality was 2.5 (95% CI 1.6-4.0) for every doubling of suPAR level. suPAR was significantly better than CRP at predicting mortality and all complications (P = 0.0036 and P = 0.0041, respectively). Combining ASA classification and suPAR level significantly improved prediction of mortality and the occurrence of a postoperative complication within 90 days after surgery (P < 0.0001)[12].

In acute medical patients, elevated suPAR is associated with increased risk of acute surgery

Acutely admitted medical patients are often fragile and in risk of future surgery. A Danish group investigated if suPAR also predicts acute surgery, which is associated with higher mortality than elective surgery, and if it predicts post-operative mortality[13]. In a retrospective registry-based cohort study of 17,312 patients, acute surgery was carried out on 2404 patients (13.9%) after a median of 45 days (IQR 5-186) following the index admission. Patients receiving acute surgery had higher baseline suPAR compared with patients receiving elective- or no surgery (p < 0.0001). The hazard ratio (HR) for acute surgery was 1.50 (95% confidence interval (CI): 1.42-1.59) for every doubling of the suPAR level in the adjusted Cox regression analysis. Death within 90 days occurred in 439 (18.3%) patients receiving acute surgery, and the adjusted HR for post-operative mortality was 1.73 (95% CI: 1.52-1.95). The authors conclude that elevated levels of suPAR in acutely admitted medical patients were **independently associated with increased risk of future acute surgery** as well as with 90-day post-operative mortality[13].

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 prognosis[4]. 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** patients[5]. The same cohort was also followed in another study, in which the suPAR plasma level was found to be an independent prognostic marker[6].

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 found[7].

In patients with **gastric cancer**, the suPAR level was significantly higher compared to healthy controls (2.3 ng/mL ± 0.77), and the suPAR level was significantly higher in cancer patients with metastatic disease (7.0 ng/mL ± 6.1) than in patients with no metastases (4.8 ng/mL ± 4.4). In the group of patients with a suPAR value above 5.2 ng/mL, the mortality was significantly increased[8].
In patients with rectal cancer[9] and colon cancer[10], 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 CRP[11].

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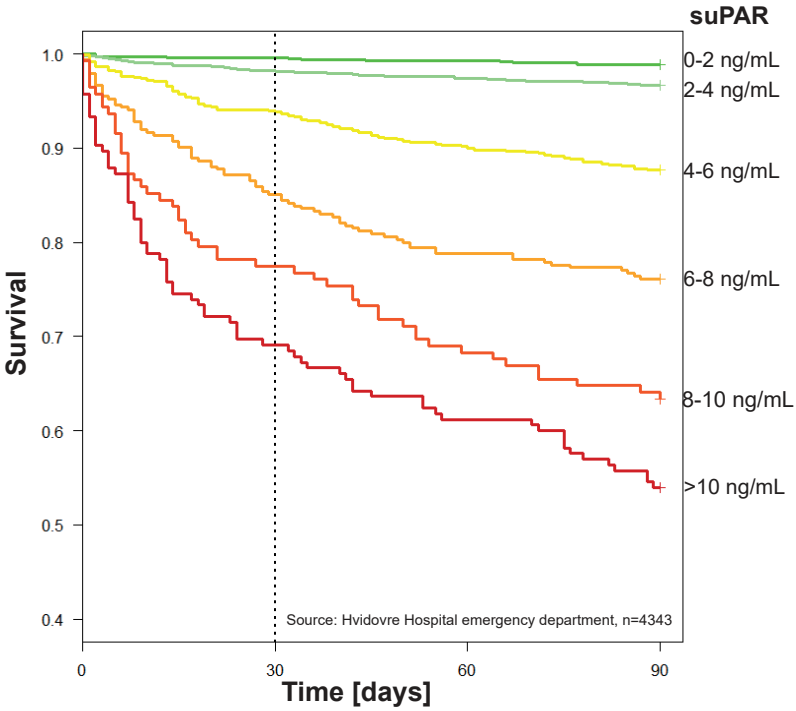
Appendix 1:

Have you considered your patient's prognosis?



Appendix 2:

suPAR level and mortality risk

Patients below the age of 70:

suPAR	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	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%

Example: In a 63-year-old patient with a suPAR level of 7.7 ng/mL the 30-day mortality risk is 7.3%; this is five times as great as the mean mortality rate (1.4%) in the age-group.

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

Appendix 3:

P-[suPAR]

Soluble urokinase plasminogen activator receptor

Unit: ng/mL Interval: 0.1-16.0

Interpretation

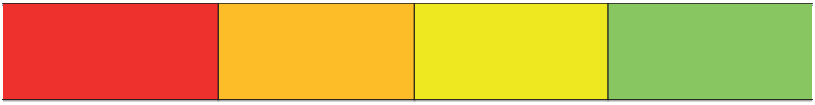
Elevated values are observed in pathological conditions and correlate with the patient's mortality risk.

- **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.

Appendix 4:



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

MODERATE RISK
Increased mortality risk
Prolonged hospital stays
Increased readmission risk

6 Infections and acute illness

Chronic diseases, e.g. COPD, diabetes, cardiovascular diseases, dementia, peptic ulcer, cancer, hepatic diseases, renal diseases

3

LOW RISK
Low mortality risk
Low readmission risk
No or well-treated comorbidities
Healthy individuals

0

Notes:

suPAR Monograph M017 UK version 3 – AUG 2019