Review

suPAR: The unspecific marker for disease presence, severity and prognosis

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ABSTRACT

Investigation of biomarkers that can promptly predict unfavourable outcome of critically illness is an emerging necessity taking into consideration the need for early intervention, the shortage of available beds in intensive care units and the considerable cost of hospitalisation. The most promising biomarker is soluble urokinase-type plasminogen activator receptor (suPAR). Three studies in large populations of critically ill patients and patients admitted to the emergency department have shown that concentrations >12 ng/mL can safely predict unfavourable outcome. This review presents a thorough analysis of the data from these studies.

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1. Introduction

At the 6th European Conference of Bloodstream Infections in Athens, Greece, on the 6–7 June 2015, data on the prognostic biomarker soluble urokinase-type plasminogen activator receptor (suPAR) were presented. A central theme of the conference was sepsis and biomarkers that may aid in clinical guidance. One session was devoted to the biomarker procalcitonin (PCT) and a clear clinical use was demonstrated: PCT can be used to guide the initiation and duration of antibiotic therapy in intensive care unit (ICU) patients with suspected sepsis. If PCT levels during monitoring remain low, withdrawal of antibiotics has no influence on mortality. Limiting antibiotic treatment duration is highly important as antibiotic overuse may cause resistance development. This is an important observation that should lead to routine use of PCT, and this was recently shown to be cost effective [1].

C-reactive protein (CRP) is the classical biomarker for bacterial infection, and PCT has similar ability to indicate bacterial infection and has stronger prognostic value. More recently, suPAR has been tested in sepsis patients. In contrast to CRP and PCT, suPAR has no diagnostic value but carries the strongest prognostic value of the three biomarkers [2,3].

2. Available evidence

suPAR was first identified by Danish researchers in the early 1990s as a marker associated with cancer and progression [4].

suPAR is the soluble form of the urokinase-type plasminogen activator receptor (uPAR), and uPAR is involved in plasminogen activation and thereby plays a role in cancer metastasis. In 2000 it was reported that suPAR was predictive for outcome in human immunodeficiency virus (HIV)-infected individuals [5]. Soon after, studies showed that suPAR also predicted outcome in bacterial infections such as tuberculosis [6] and pneumococcal pneumonia [7] as well as in parasitic infection with malaria [8]. Thus, suPAR appeared to have broad unspecific prognostic significance and is likely to mirror the inflammatory responses of the host towards the invading pathogen. The higher the suPAR, the more severe the response to infection and the worse the outcome.

Inflammation is thought to be a driver of disease, also in the general non-diseased population. Subclinical chronic or low-grade inflammation, as measured by slightly elevated CRP levels, pro-inflammatory cytokines, or an elevated and activated number of white blood cells, may be markers of chronic inflammation. As suPAR is also elevated by inflammatory conditions, and because it is a very stable molecule both in vivo [9] and in vitro [10], we speculated whether suPAR could be a marker of disease development in the general population. In a population study of 2602 Danish citizens, it was found that suPAR was predictive of several common diseases of the general population, such as cardiovascular disease, type 2 diabetes and various types of cancer [11].

suPAR has potential as a prognostic marker in the ICU (as reviewed in [12,13]). A multistep approach was followed to develop the role of suPAR for the early prognosis of sepsis. At first, a study was conducted in a Greek population of 180 patients hospitalised in the ICU with ventilator-associated pneumonia and sepsis [14]. suPAR was measured within the first 24 h from diagnosis and

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concentrations >12.9 ng/mL could predict death in the first 28 days. Cox regression analysis confirmed the significance of suPAR and Acute Physiology and Chronic Health Evaluation (APACHE) II score as the only independent parameters associated with unfavourable outcome [14].

These findings were further developed in the largest study to date, including 1914 patients with sepsis [15]. Patients were enrolled from departments participating in the Hellenic Sepsis Study Group. Patients were hospitalised either in the general ward or in the ICU. Blood was sampled for suPAR measurement in the first 24 h from diagnosis of an infection with signs of the systemic inflammatory response syndrome. It was found that suPAR ≥12 ng/mL was linked with >80% sensitivity and 94.5% negative predictive value for unfavourable outcome. This cut-off was used to improve prognostication by APACHE II. Indeed, four grades of prediction could be developed: a low APACHE II score (<17) and low suPAR (<12 ng/mL) where 28-day mortality was 5.5%; and low APACHE II (<17) but high suPAR (≥12 ng/mL) where 28-day mortality was 17.4% Similarly, in patients with high APACHE II score but low suPAR, mortality was 37.4%, whilst patients with both high suPAR and high APACHE II score had a mortality >50%. In the same publication, this strong discriminative prognostic score developed in Greek patients was validated in a cohort of Swedish patients [15].

There is no doubt that suPAR has strong prognostic value in ICU patients. However, in many cases this knowledge may not lead to lifesaving interventions, as limited treatment options are efficient in severely ill sepsis patients. But one crucial measure is early and correct identification of high-risk patients in need of early intervention [16]. The earliest contact with the patient is often in the emergency department (ED), and with the unspecific and strong prognostic value of suPAR, it makes sense to carry out the measurement as early as possible.

This was investigated in the ED at North Zealand University Hospital in Denmark (TRIAGE-study) [17]; 5992 patients admitted to the ED from September 2013 to December 2013 were included in the study. Mean patient age was 59.8 years and 50.1% were female. The mean (± standard deviation) concentration of suPAR was 5.5 ± 3.6 ng/mL. Mortality at 30 days was 3.6%. Receiver operating characteristic (ROC) curve analyses of the prognostic value of suPAR in relation to 30-day mortality showed that the area under the curve (AUC) was 0.85 (95% confidence interval 0.82–0.87). Cox regression analysis of 30-day mortality in relation to suPAR quartiles showed that the hazard ratio (HR) was 2.2 for the second quartile, 6.5 for the third quartile and 38.4 for the highest quartile ($P < 0.001$). In a multivariate analysis including sex, age, CRP, leucocyte count and triage category, suPAR remained a strong independent predictor of 30-day mortality with a HR of 4.5 for the second quartile, 8.3 for the third quartile and 26.9 for the highest quartile ($P < 0.001$).

Thus, in a large unselected population of acute medical patients, suPAR levels are strongly and independently associated with disease severity and mortality, indicating that suPAR adds information to established prognostic indicators. Whilst patients with low suPAR levels have a low risk of mortality, patients with high suPAR levels should receive a high level of clinical attention.

3. Conclusions

Owing to the prognostic abilities of the suPAR biomarker, Copenhagen University Hospital Hvidovre in Denmark decided in November 2013 to implement suPAR as a routine biomarker measured on all acute medical patients when they arrive at the ED. In conclusion, suPAR is an unspecific prognostic biomarker that displays prognostic ability above and beyond traditional specific and diagnostic biomarkers. As early recognition of severely ill patients is crucial for outcome, suPAR may have most value in the acute care or emergency department, assisting the clinical decision of whether to admit a patient or not, as well as in identification of patients with high risk of a negative outcome where urgent clinical intervention is needed.

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