Soluble urokinase plasminogen activation receptor - An emerging new biomarker of cardiovascular disease and critical illness

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ABSTRACT

Soluble urokinase plasminogen activation receptor (suPAR) is an emerging new biomarker, which has been shown to not only correlate with traditional biomarkers but also outperform CRP at prognosticating CVD. More clinical trials on suPAR is in the future research agenda.

Key words: Biomarkers; Cardiovascular disease; Critical illness; Heart failure

INTRODUCTION

The pathogenesis of cardiovascular disease (CVD) is multifactorial. Conventional risk factors such as cigarette smoking, diabetes, hyperlipidemia, and hypertension are absent in 15–20% of patients with CVD.[1] Given the established role of chronic inflammation in patients with CVD, the identification of serum biomarkers, which may aid in early intervention and risk prediction has been of increasing importance. Biomarkers including N-terminal probrain natriuretic peptide, urine albumin/creatinine ratio, and high sensitivity C-reactive protein (CRP) have been recognized as strong predictors of adverse cardiovascular outcomes.[2,3]

Soluble urokinase plasminogen activation receptor (suPAR) is an emerging new biomarker, which has been shown to not only correlate with traditional biomarkers but also outperform CRP at prognosticating CVD.[4,5] Urokinase-type plasminogen activator receptor (uPAR) is a membrane-linked protein, found in several cell types including immunologic and vascular endothelial cells. It comprised three domains (D1, D2, and D3) and is anchored to the cell membrane by a glycosylphosphatidylinositol molecule

attached to D3. Biologically, uPAR is involved in the regulation of atherogenesis and plays a role in cell migration, adhesion, angiogenesis, fibrinolysis, and cell proliferation. The uPAR molecule may undergo cleavage into three soluble forms (suPAR), the full-length D1 D2 D3 molecule and the fragments D1 and D2 D3. The physiologic function of suPAR is not as well understood; however, suPAR levels correlate with proinflammatory markers such as tumor necrosis factor, and it has been associated with endothelial dysfunction, neo-intimal formation of atherosclerosis, and plaque destabilization. It is also associated with conventional CVD risk factors including smoking and physical inactivity; however,

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unlike CRP, it has not been linked to obesity. Compared to other inflammatory markers, suPAR is not an acute phase reactant, with levels remaining stable even during acute cardiac events such as acute myocardial infarction. It exhibits limited circadian variation and generally tends to be higher in women despite lower CVD risk compared to men.[4,6]

The Danish MONICA 10 cohort is one of the largest to be investigated for the predictive value of suPAR in CVD. In this population, an elevated suPAR level was associated with an increased risk of cancer, CVD, Type 2 diabetes mellitus, and mortality.[7] After adjustment for Framingham Risk Score (FRS) variables, women with suPAR levels in the highest tertile had a 1.74-fold (95% confidence interval [CI]: 1.08–2.81) and men had a 2.09-fold (95% CI: 1.37–3.18) increase in CVD risk compared to the lowest tertile. Inclusion of both suPAR and CRP in the model resulted in stronger risk prediction with a 3.30-fold (95% CI: 1.36–7.99) increase for women and a 3.53-fold (1.78–7.02) increase for men when both biomarkers were in the highest compared to the lowest tertile. In men, the C statistics improved significantly from 0.722 (95% CI: 0.686–0.757) when tertile levels of suPAR (0.733, 95% CI: 0.699–0.769), CRP (0.734, 95% CI: 0.699–0.769) and their combination (0.737, 95% CI: 0.703–0.772) were added to FRS. Reclassification of individuals (risk of composite outcome in 10 years of <10%, 10–20%, and >20%) measured by the net reclassification index (NRI) and integrated discrimination improvement (IDI) was profoundly improved with the addition of suPAR into the risk model for men (NRI: 51%, 95% CI: 0.240, 0.772; IDI: 1.6%, 95% CI: 0.005–0.026) and for women (NRI: 57%, 95% CI: 0.253-0.889; IDI: 1.2%, 95% CI: 0.003–0.021). Favorable, but less robust results were observed for CRP only among men (NRI: 31%, 95% CI: 0.081–0.534; IDI: 1.8%, 95% CI: 0.008–0.028).[5]

With regard to patients with established CVD, data supporting the utility of suPAR in coronary artery disease (CAD) have shown that elevated levels of plasma suPAR are associated with the presence and severity of CAD ($P < 0.0001$) and are independent predictors of death (hazard ratio [HR]: 2.62; $P < 0.0001$) and myocardial infarction (HR: 3.2; $P < 0.0001$).[8] This has also been proven in cerebrovascular diseases, where suPAR was associated with increased occurrence of carotid plaque HR: 1.51 (95% CI: 1.05–2.17) and increased incidence of ischemic stroke (HR: 2.21 (95% CI: 1.52–3.22).[9]

The importance of suPAR in critical illness, especially sepsis, has also garnered a lot of interest. Among critically ill patients, it appears to be of less diagnostic utility compared to other biomarkers. For instance, Koch *et al.* found that in a cohort of 273 critically ill patients (197 with sepsis, 73 without sepsis), suPAR levels were higher than in healthy controls. However, the area under the receiver operating characteristic curve for predicting sepsis was only 0.62 for suPAR compared to 0.86 and 0.78 for CRP and procalcitonin. On the other hand, the prognostic value of suPAR among critically ill patients is inconclusive. In the aforementioned study by Koch *et al.*, suPAR levels correlated with disease severity scores and low levels of suPAR at hospital days 3 and 7 predicted improved Intensive Care Unit and overall survival.[10] Data from Jalkanen *et al.*[11] found that the highest concentration quintiles were associated with poor outcome in patients with out-patient cardiac arrest admitted to critical care units; however, suPAR alone had inadequate predictive value for poor outcome and did not associate with 12-month neurological outcome.

Based on the current literature, suPAR is a promising biomarker of chronic inflammation and subclinical organ dysfunction with proven prognostic value in CVD and critical illness. However, further research is necessary before acceptance into clinical practice, especially with regard to CVD. First, whether suPAR has a causal role in CVD or whether it is merely a marker of underlying disease is still uncertain. A better understanding of the regulation of suPAR and its interaction with other biomarkers may help explain some of the current discrepancies such as the lack of an association with obesity and the higher levels observed in women compared to men. At this time, there are also no well-validated cut-off values and no established therapies that target suPAR levels. Furthermore, the studies evaluating suPAR have been conducted in predominantly Caucasian individuals, which pose significant selection bias and limit the generalizability of findings. We will likely see more outcome data with suPAR in the future, adding to the evergrowing body of knowledge of biomarkers in cardiovascular disease and critical illness.

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Conflicts of interest
There are no conflicts of interest.

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11. Jalkanen V, Vaahersalo J, Pettilä V, Kurola J, Varpula T, Tiainen M, *et al.* The predictive value of soluble urokinase plasminogen activator receptor (SuPAR) regarding 90-day mortality and 12-month neurological outcome in critically ill patients after out-of-hospital cardiac arrest. Data from the prospective FINNRESUSCI stud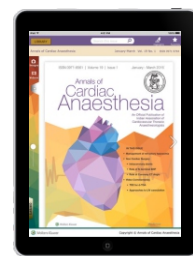y. Resuscitation 2014;85:1562-7.