Soluble Urokinase Plasminogen Activator Receptor for Risk Prediction in Patients Admitted with Acute Chest Pain

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BACKGROUND: Plasma concentrations of soluble urokinase plasminogen activator receptor (suPAR) predict mortality in several clinical settings, but the long-term prognostic importance of suPAR in chest pain patients admitted on suspicion of non–ST-segment elevation acute coronary syndrome (NSTEACS) is uncertain.

METHODS: suPAR concentrations were measured on admission in 449 consecutive chest pain patients in a single center between January 3, 2005, and February 14, 2006. Patients were followed for all-cause mortality from discharge until July 28, 2011.

RESULTS: The diagnoses at discharge comprised high-risk NSTEACS [non–ST elevation myocardial infarction or unstable angina with electrocardiogram (ECG) abnormalities] in 77 patients (17.2%) and low-risk NSTEACS without evidence of myocardial ischemia in 257 (57.2%) of patients. Another 115 (25.6%) of patients received other diagnoses. During a median follow-up of 5.7 years (range, 0.01–6.6 years) there were 162 (36.1%) deaths. suPAR was predictive of mortality independent of age, sex, smoking, final diagnosis for the hospitalization, comorbidities (diabetes, hypertension, previous myocardial infarction, and heart failure), and variables measured on the day of admission (renal function, inflammatory markers, and markers of myocardial ischemia) with a hazard ratio (95% CI) of 1.93 (1.48–2.51) per SD increase in log-transformed suPAR, \( P < 0.0001 \). The use of suPAR improved the predictive accuracy of abnormal ECG findings and increased troponin concentrations regarding all-cause mortality (c statistics, 0.751–0.805; \( P < 0.0001 \)).

CONCLUSIONS: suPAR is a strong predictor of adverse long-term outcomes and improves risk stratification beyond traditional risk variables in chest pain patients admitted with suspected NSTEACS.

The postdischarge management of acute chest pain patients admitted for suspected non–ST-segment elevation acute coronary syndrome (NSTEACS)7 remains a clinical challenge. The common denominator of acute chest pain reflects a heterogeneous blend of diagnoses with varying prognoses, and only a minority of patients with suspected NSTEACS are subsequently diagnosed with non–ST-elevation myocardial infarction (NSTEMI). New diagnostic tools may help uncover important pathologies that are otherwise overlooked in the clinical evaluation of these patients during their hospital stay.

Risk assessment of patients with suspected NSTEACS currently relies on medical history, electrocardiogram (ECG), and troponin measurements. Integrated risk scoring systems such as the Global Registry of Acute Coronary Events (GRACE) and the Thrombolysis in Myocardial Infarction (TIMI) risk scores have shown better predictive accuracy for major adverse cardiac events at up to 6 months in unselected chest pain patients than ECG and troponins alone (1). These and other clinical risk algorithms were mainly developed for the purpose of identifying patients with high-risk ACS. However, patients in whom ACS is initially ruled out may still carry a relatively poor prognosis with respect to future morbidity and mortality for both cardiovascular and noncardiovascular causes (2).

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1 Nonstandard abbreviations: NSTEACS, non–ST-segment elevation acute coronary syndrome; NSTEMI, non–ST-elevation myocardial infarction; ECG, electrocardiogram; GRACE, Global Registry of Acute Coronary Events; TIMI, Thrombolysis in Myocardial Infarction; suPAR, soluble urokinase plasminogen activator receptor; CVD, cardiovascular disease; PCI, percutaneous coronary intervention; TnT, cardiac troponin T; HF, heart failure; ICD, International Classification of Disease; CHF, congestive heart failure; CK-MB, creatinine kinase MB; CRP, C-reactive protein; NRI, net reclassification improvement; IDI, integrated discrimination improvement; LDL-C, LDL cholesterol; HR, hazard ratio; LVEF, left ventricular ejection fraction.
Therefore, new biomarkers that are simple to measure and improve risk stratification for the entire spectrum of acute chest pain patients are warranted to guide the use of any interventional measures. Soluble urokinase plasminogen activator receptor (suPAR) is an inflammatory biomarker, which is released into the circulation by cleavage of the membrane-bound uPAR from various cells, including inflammatory and endothelial cells. uPAR and suPAR have been implicated in atherogenesis because of their roles in orchestrating cellular adhesion, migration, and proliferation during tissue remodelling in the atherosclerotic plaque. suPAR is intimately linked to these processes and has therefore been suggested as a marker of low-grade inflammation. Increased circulating concentrations of suPAR are strongly associated with increased risk of cardiovascular disease, diabetes, cancer, and mortality in the general population, with poor outcomes in critically ill patients, and with recurrent MI and mortality in patients with STEMI undergoing primary percutaneous coronary intervention (PCI). In the present retrospective cohort study, we investigated whether suPAR was also an independent marker of outcome in chest pain patients admitted with suspected NSTEACS.

**Methods**

**STUDY POPULATION**

The study population included 538 consecutive patients admitted with acute chest pain and suspected NSTEACS at a single regional Danish hospital between January 3, 2005, and February 14, 2006. In Denmark, patients with suspected STEMI are immediately transferred for primary PCI, and therefore these patients were not part of the present study. Blood samples and complete follow-up data for the current study were available from 449 patients. High-risk NSTEACS was diagnosed if patients had ischemic changes in the ECG (ST depression or negative T waves) and/or increased cardiac troponin T (TnT) as described previously. The diagnostic criteria were based on recommendations in recent guidelines. Information regarding clinical variables was obtained from patients’ charts. All patients gave their written informed consent to their participation in the study. The study complied with the Declaration of Helsinki and was approved by the local ethics committee.

**OUTCOME EVENTS AND FOLLOW-UP**

The endpoints for this study were all-cause mortality and a combined endpoint of fatal and nonfatal MI. Information about deaths was obtained from the Danish Civil Central Register, which records the vital status of all inhabitants in Denmark. Information about readmissions with MI [International Classification of Disease (ICD) codes I21.0 to I21.9] and heart failure (ICD I50 to I50.9) was obtained from discharge codes from the Danish National Hospital Register, a database of all nonpsychiatric hospitalizations. Patients were followed from discharge until July 28, 2011.

**DEFINITION OF INDEX DIAGNOSIS AND ECG ANALYSES**

The discharge diagnoses were grouped according to (a) high-risk NSTEACS, (b) low-risk NSTEACS (suspected high risk NSTEACS that did not fulfill the diagnostic criteria), (c) other cardiac diseases [e.g., arrhythmias, congestive heart failure (CHF)], and (d) noncardiac diseases [e.g., infectious diseases, stroke, uremia]. The ECGs at admission were analyzed by one investigator (K.K. Iversen), who was blinded to follow-up data, and were divided into normal ECGs and abnormal ECGs (signs of acute or previous ischemic heart disease, i.e., Q-waves, ST-depression, T-wave inversion, or bundle-branch block). A recent study has suggested the validity of this distinction of ECG changes for prediction of adverse coronary events.

**LABORATORY ANALYSES**

Blood samples were taken at baseline and typically repeated every 6–8 h until the concentrations of biomarkers reflecting myocardial necrosis [TnT and/or creatinine kinase MB (CK-MB)] either consistently decreased (typically after 3 sequential blood samples) or remained within the reference interval (typically after 2 sequential blood samples). The following assays were used locally during admission for ruling out MI: third generation Elecsys troponin T immunoassay (product number 12017644122 with a lower limit of detection of 10 ng/L and a CV of 10% at a TnT concentration of 30 ng/L) and CK-MB (both Roche Diagnostics). Blood samples for subsequent analyses were centrifuged for 10 min at 3 000 rpm, and plasma was stored at −20 °C until analysis. Plasma concentrations of high-sensitivity C-reactive protein (CRP) and suPAR were measured from thawed biobanked samples using commercially available kits according to the manufacturers’ instructions (CRPus KRYPTOR kit (detection limit, 0.06 mg/L) (BRAHMS AG) and suPARnostic® kit (validated to measure suPAR concentrations between 0.6 and 22 ng/mL) (ViroGates)). Both CRP and suPAR have previously been shown to be stable in frozen samples.

**STATISTICAL ANALYSES**

Tests for differences between groups were done by ANOVA and the χ² test for continuous and discrete variables, respectively. Differences of plasma suPAR concentrations on admission between individuals with and without adverse events were compared with the
Results

BASELINE CHARACTERISTICS AND CORRELATIONS

Baseline characteristics for the 449 patients overall and divided into tertiles of suPAR concentrations are shown in Table 1. Patients presenting with high suPAR concentrations were characterized by high-risk features such as increasing age, a higher prevalence of cardiovascular risk factors exemplified by increased concentrations of LDL cholesterol (LDL-C), blood glucose, creatinine, TnT; higher rate of smoking; and previous CVD. The relations of suPAR to these risk factors analyzed by univariate, and age- and sex-adjusted Pearson correlation analyses are presented in Table A in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol59/issue11. By multiple linear regression analysis with log(suPAR) as the dependent variable, the explanatory variables age, sex, diabetes, hypertension, smoking status, previous MI, and CHF and baseline concentrations of creatinine, LDL-C, HDL-C, CRP, and TnT accounted for less than half of the variability in suPAR concentrations ($R^2 = 0.48$).

DIAGNOSIS ON ADMISSION AND DURING FOLLOW-UP

The final diagnosis at discharge was high-risk NSTEACS in 77 (17.2%) and low-risk NSTEACS in 257 (57.2%) of patients, whereas 58 (12.9%) of patients had another cardiovascular diagnosis such as arrhythmia, CHF, or significant valve disease. In total, 57 (12.7%) had a non–cardiac-related diagnosis (e.g., pneumonia, gastrointestinal causes, or musculoskeletal disorders). The distribution of suPAR tertiles according to the index diagnosis is shown in Fig. 1.

During a median follow-up of 5.7 years (range 0.01–6.6 years), there were 162 (36.1%) deaths, 46 (10.2%) readmissions due to HF, and 89 (19.8%) cases of fatal or nonfatal MI. Of patients who died during follow-up, 96 deaths were related to cardiovascular diseases (ICD I00 to I19), which included 40 fatal MIs (ICD I21 to I22) and 4 deaths due to HF (ICD I50 to I50.9) as the primary diagnoses. Nineteen deaths were registered as cancer (CD C00 to D48) and 17 fatalities were due to infection or pulmonary diseases (ICD A40 to A40.5, J10 to J18.9, and J40 to J46.9) as the primary diagnosis.

BLOOD SAMPLING

The median (interquartile range) time from onset of symptoms to admission was 6.5 h (2.5–18.9 h), and the time from symptom onset to first blood sampling was 7.7 h (3.7–20.8 h), whereas the time from admission to baseline blood sample was 0.8 h (0.2–2.0 h). The number of consecutive blood samples taken during admission varied as follows: 1 blood sample (8.2% of entire cohort), 2 samples (28.5%), 3 samples (62.4%), ≥4 samples (9.0%).

suPAR and ALL-CAUSE MORTALITY

Patients who died in the follow-up period had significantly higher suPAR concentrations at baseline than surviving patients (median 5.99 vs 4.11 mg/L; $P$ for difference <0.0001) (see online Supplemental Fig. A). As illustrated in Fig. 2A, all-cause mortality increased significantly during follow-up from 17.1% to 51.8% across increasing tertiles of age- and sex-adjusted suPAR concentrations, $P < 0.0001$. In a univariate model, suPAR concentrations were significantly asso-
associated with all-cause mortality [hazard ratio (HR) 2.73 (95% CI, 2.32–3.22) per SD increment in log(suPAR); P < 0.0001]. In a model adjusted for age and sex, suPAR remained strongly associated with all-cause mortality [HR 2.21 (1.84–2.65); P < 0.0001], and further adjustments for the final index diagnosis, diabetes, hypertension, smoking, CHF, previous MI, and admission concentrations of log-transformed plasma creatinine, CRP, and TnT in the fully adjusted model did not considerably attenuate this relationship [HR 1.93 (1.48–2.51); P < 0.0001] (Table 2).

Finally, when suPAR was included in the same model as CRP, adjusted for age and sex, CRP was only weakly related to outcomes [HR 1.21 (1.01–1.45) per SD increment in log(CRP); P = 0.042 vs HR 2.08 (1.69–2.56) per SD increment in log(suPAR); P < 0.0001], and in the fully adjusted model, CRP did not predict mortality (P = 0.16).

### Table 1. Baseline characteristics for the entire cohort and divided in tertiles of the concentration of the first available suPAR sample.a

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>suPAR (1–27.3 ng/mL)</th>
<th>First suPAR tertile (1.0–4.0 ng/mL)</th>
<th>Second suPAR tertile (4.0–5.5 ng/mL)</th>
<th>Third suPAR tertile (5.5–27.3 ng/mL)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>449</td>
<td>67 (57–78)</td>
<td>149 58 (48–67)</td>
<td>150 71 (61–78)</td>
<td>150 76 (65–83)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>449</td>
<td>56.8</td>
<td>149 67.1</td>
<td>150 52.0</td>
<td>150 51.3</td>
<td>0.008</td>
</tr>
<tr>
<td>Hemodynamic parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>443</td>
<td>150 (130–172)</td>
<td>146 150 (132–170)</td>
<td>150 149 (131–172)</td>
<td>147 150 (126–178)</td>
<td>0.79</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>442</td>
<td>83 (72–93)</td>
<td>146 84 (75–98)</td>
<td>150 82 (70–91)</td>
<td>145 81 (70–92)</td>
<td>0.008</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>168</td>
<td>50 (35–60)</td>
<td>44 55 (43–60)</td>
<td>58 60 (40–60)</td>
<td>66 40 (30–50)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>436</td>
<td>17.7</td>
<td>146 10.3</td>
<td>144 13.9</td>
<td>146 28.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>413</td>
<td>54.2</td>
<td>143 47.6</td>
<td>142 56.3</td>
<td>128 59.4</td>
<td>0.12</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>433</td>
<td>38.8</td>
<td>145 35.9</td>
<td>144 41.0</td>
<td>144 39.6</td>
<td>0.51</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>443</td>
<td>28.9</td>
<td>147 18.4</td>
<td>149 28.2</td>
<td>147 40.1</td>
<td>0.0002</td>
</tr>
<tr>
<td>Prior CHF, %</td>
<td>435</td>
<td>25.3</td>
<td>146 15.1</td>
<td>146 24.0</td>
<td>143 37.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Laboratory values</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First suPAR value, ng/mL</td>
<td>449</td>
<td>4.6 (3.59–6.06)</td>
<td>149 3.18 (2.68–3.59)</td>
<td>150 4.54 (4.22–4.97)</td>
<td>150 7.02 (6.06–8.40)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak suPAR value, ng/mL</td>
<td>449</td>
<td>4.8 (3.81–6.34)</td>
<td>149 3.39 (2.91–3.79)</td>
<td>150 4.73 (4.33–5.21)</td>
<td>150 7.21 (6.25–9.02)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>430</td>
<td>6.17 (1.94–20.6)</td>
<td>143 2.49 (1.01–6.49)</td>
<td>145 6.05 (2.17–14.4)</td>
<td>142 18.8 (6.09–51.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>406</td>
<td>4.8 (3.9–5.7)</td>
<td>144 4.9 (4.2–5.9)</td>
<td>134 5.0 (4.0–5.6)</td>
<td>128 4.7 (3.5–5.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>403</td>
<td>2.8 (2.0–3.6)</td>
<td>144 3.0 (2.4–3.8)</td>
<td>133 2.8 (2.0–3.6)</td>
<td>126 2.6 (1.7–3.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>404</td>
<td>1.3 (1.0–1.7)</td>
<td>144 1.3 (1.1–1.7)</td>
<td>133 1.4 (1.1–1.8)</td>
<td>127 1.3 (0.9–1.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>403</td>
<td>1.3 (0.9–1.9)</td>
<td>142 1.3 (0.9–2.1)</td>
<td>133 1.4 (1.0–1.9)</td>
<td>128 1.3 (0.9–1.8)</td>
<td>0.83</td>
</tr>
<tr>
<td>Creatinine, µmol/L</td>
<td>443</td>
<td>77 (64–94)</td>
<td>148 72 (61–83)</td>
<td>149 76 (64–87)</td>
<td>146 91 (70–125)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose</td>
<td>424</td>
<td>5.8 (5.2–7.1)</td>
<td>146 5.5 (5.1–6.2)</td>
<td>138 5.9 (5.2–6.8)</td>
<td>140 6.5 (5.4–8.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak TnT value, ng/L</td>
<td>446</td>
<td>10 (10–80)</td>
<td>149 10 (10–10)</td>
<td>149 10 (10–50)</td>
<td>148 40 (10–250)</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

* Data are presented as median (interquartile range) for continues variables and proportions in percent for categorical variables. The P values were calculated on the basis of linear trends for all continuous variables and nonparametric testing for categorical variables.
follow-up (adjusted for age and sex) for both the outcome of readmission due to heart failure (increase from 3.2% in the lowest suPAR tertile to 26.6% in the highest tertile) and nonfatal or fatal MI (10.5% in the lowest suPAR tertile increasing to 38.6% in the highest tertile), both $P < 0.0001$ (Fig. 2B).

suPAR concentrations were highly significantly associated with readmissions due to HF and the composite outcome of recurrent fatal or nonfatal MI both in univariate analysis and in a model adjusted for age and sex (Table 2; all $P < 0.0001$). In the fully expanded model (including age, sex, final index diagnosis, diabetes, hypertension, smoking, CHF, previous MI, and admission concentrations of log-transformed plasma creatinine, CRP, and TnT) suPAR predicted only readmission due to HF (Table 2) [HR per SD increment in log(suPAR) for HF, 2.00 (95% CI 1.26–3.18); $P = 0.004$], whereas suPAR did not predict the composite outcome unless final index diagnosis and TnT were omitted from the model [HR 1.46 (1.07–1.97); $P = 0.017$]. The predictive capability of suPAR (adjusted for age and sex) was not attenuated with the use of the first available blood sample compared to the peak concentration with respect to either outcome [HF, first suPAR sample HR 2.24 (0.64–7.77), peak concentrations of suPAR HR 1.20 (0.36–4.01); fatal or nonfatal MI, first suPAR sample HR 1.81 (1.43–2.29), peak concentrations of suPAR HR 1.78 (1.42–2.23)].

**suPAR, ECG, AND TNT**

The presence of suPAR concentrations above or below the median at admission added significant prognostic information to findings of an abnormal ECG or increased (>100 ng/L) concentrations of TnT (Fig. 3). Patients with increased suPAR concentrations had a significantly worse prognosis than patients with low suPAR values. This was evident for both low- and high-
risk individuals, as assessed by the ECG and peak TnT concentrations during admission. Thus, c statistics for all-cause mortality increased from 0.751 (95% CI, 0.713–0.789) to 0.805 (0.772–0.837) (P for difference <0.0001) with the addition of plasma suPAR concentrations to a model consisting of age, sex, and presence of abnormal ECG and increased (>100 ng/L) peak TnT concentrations.

Table 2. Association between suPAR and outcome.¹

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Univariate model</th>
<th>Multivariate model 1</th>
<th>Multivariate model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2.73 (2.32–3.22)</td>
<td>&lt;0.0001</td>
<td>2.21 (1.84–2.65)</td>
</tr>
<tr>
<td>Readmission for HF</td>
<td>2.69 (1.98–3.67)</td>
<td>&lt;0.0001</td>
<td>2.33 (1.67–3.27)</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>1.98 (1.59–2.46)</td>
<td>&lt;0.0001</td>
<td>1.81 (1.43–2.29)</td>
</tr>
</tbody>
</table>

¹ Standardized HRs for log(suPAR) for all-cause mortality and fatal or nonfatal MI in 3 (1 univariate and 2 multivariate) Cox proportional hazard models. Multivariate model 1, adjusted for age and sex; multivariate model 2, adjusted for model 1 + final index diagnosis, diabetes, hypertension, smoking, previous MI, CHF, and log transformed plasma creatinine, CRP, and peak concentrations of TnT.

Fig. 3. suPAR and outcome in patients according to ECG and TnT findings.
Outcome according to the presence of ECG abnormalities (A) or peak TnT concentrations (B) with first available suPAR concentrations below or above the median. The number of events/total number of individuals is shown in each bar.
suPAR was a significant predictor of fatal and nonfatal MI, when adjusted for age and sex (Table 3). When suPAR had significant predictive capabilities only with respect to the combined outcome of fatal and nonfatal cause mortality early in the follow-up period. With respect to the combined outcome of fatal and nonfatal MI, suPAR did not vary substantially over time, although there was a trend toward a stronger predictive capability of suPAR for the outcome of all-cause mortality early in the follow-up period. It is evident from Table 3 that for all 3 outcomes the predictive capabilities of suPAR at different time points during follow-up, the HR for the outcome after 6 months until 5 years adjusted for age and sex improved substantially, from 0.744 (95% CI, 0.706–0.783) to 0.744 (95% CI, 0.706–0.783) (P < 0.0001), respectively (see online Supplemental Table B). When suPAR was added to the fully expanded model with traditional cardiovascular risk factors, the c statistics improved significantly, from 0.814 (0.776–0.852) to 0.830 (0.795–0.865) (P for difference = 0.047). Addition of suPAR to the fully expanded model also led to significant improvements for NRI, by 0.287 (P = 0.029), and IDI, by 0.026 (P = 0.027). The corresponding numbers for patients readmitted with HF and with the combined outcome of fatal or nonfatal MI is shown in online Supplemental Table B.

**PREDICTIVE CAPABILITIES OF suPAR WITH INDEX DIAGNOSIS AND TIME**

We found no interaction between the adjudicated diagnoses at discharge and the predictive capability of suPAR during follow-up for the outcome of all-cause mortality. To determine trends in the predictive capability of suPAR during follow-up, we calculated the HR for the outcome after 6 months and 1, 3, and 5 years adjusted for age and sex. It is evident from Table 3 that for all 3 outcomes the predictive capabilities of suPAR did not vary substantially over time, although there was a trend toward a stronger predictive capability of suPAR for the outcome of all-cause mortality early in the follow-up period. With respect to the combined outcome of fatal and nonfatal MI, suPAR had significant predictive capabilities only in the model adjusted for age and sex (Table 3). When TnT was omitted from the fully expanded model, suPAR was a significant predictor of fatal and nonfatal MI after 1 year (data not shown).

**Discussion**

This is the first study to demonstrate that suPAR concentrations measured in the first blood sample upon admission in patients with chest pain and suspected NSTEACS is a strong and independent mid- and long-term predictor of all-cause mortality and to a lesser extent MI. Importantly, this effect was independent of the final discharge diagnosis. Even after adjustments for age and sex, patients with a suPAR concentration in the lowest tertile had a relatively good prognosis, with a mortality of 2.6% after 6 months and 17.5% after 6 years of follow-up, whereas the corresponding numbers for patients in the highest suPAR tertile were considerably less favorable, with mortality rates of 11.2% and 42.7%, respectively. suPAR was also a strong predictor of future readmissions due to HF and to a lesser degree also predicted future MI, although this effect disappeared when TnT and final index diagnosis were included in the fully expanded model.

The predictive capability of suPAR for all-cause mortality, HF, and MI was preserved whether first blood sample concentrations or peak concentrations of suPAR were used. Thus, the exact timing of blood sampling for clinical use of suPAR for risk prediction in these acute chest pain patients does not seem to be important. Therefore, these biomarker characteristics could make suPAR a strong and suitable candidate in management decisions regarding acute chest pain patients with suspected NSTEACS.

The current practice for the evaluation of acute chest pain patients with suspected NSTEACS is based on serial ECG analyses and troponin measurements. Although the prognosis in NSTEACS patients is clearly dependent on ECG abnormalities and increased plasma troponin concentrations (23), many acute chest pain patients have underlying pathologies that do not involve significant coronary artery disease. Under such circumstances an unremarkable clinical assessment and test results could often result in swift discharge of patients, with potentially serious adverse outcomes. Thus, addi-

**Table 3. Association between suPAR and outcome during follow-up.**

<table>
<thead>
<tr>
<th>Model</th>
<th>Outcome</th>
<th>6 months</th>
<th>1 year</th>
<th>3 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivariate model 1</td>
<td>All-cause mortality</td>
<td>2.88 (2.02–4.11)</td>
<td>&lt;0.0001</td>
<td>2.98 (2.26–3.92)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>HF readmission</td>
<td>1.87 (1.36–2.57)</td>
<td>&lt;0.0001</td>
<td>2.14 (1.54–2.99)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Fatal or nonfatal MI</td>
<td>2.05 (1.46–2.88)</td>
<td>&lt;0.0001</td>
<td>2.00 (1.48–2.72)</td>
<td>&lt;0.0001</td>
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* Standardized HRs for log(suPAR) for all-cause mortality, HF, and fatal or nonfatal MI in a Cox proportional hazard model adjusted for age and sex (multivariate model 1) from 6 months until 5 years of follow-up.
tional variables are needed for optimal treatment of acute chest pain patients with suspected NSTEACS, especially when MI has been ruled out. In our cohort only about 25% ultimately had high-risk NSTEACS, which may have suggested that the remaining population had a low risk. Measurements of suPAR and subsequent correlation with long-term mortality on admission nevertheless showed that this was not the case. Application of a strategy in which suPAR concentrations were considered together with ECG abnormalities and increased concentrations of TnT resulted in improved risk stratification for all-cause mortality and MI both in low-risk patients (with or without NSTEACS) with normal ECG findings and TnT concentrations within reference intervals, and in high-risk individuals with abnormal ECGs and TnT concentrations above reference intervals, respectively. This suggests that suPAR may contribute to clinical decision-making, particularly at the time of discharge of apparently low-risk acute chest pain patients, in whom low suPAR values may add considerable weight to an expected low long-term morbidity and mortality. The clinical implications of increased suPAR concentrations (apart from worsened prognosis), however, remain unknown; at a minimum this finding may warrant a thorough follow-up, with additional clinical and paraclinical workups in pursuit of significant pathology together with modifications of risk factors such as smoking, physical inactivity, and obesity. Prospective studies are warranted to study the results of a suPAR-dependent clinical strategy in patients with acute chest pain and suspected NSTEACS. Such studies would be important to establish appropriate cutoff values for suPAR and to examine the effects of diagnostic and therapeutic interventions in such high-risk individuals.

Patients with high concentrations of suPAR on admission were characterized by high-risk features such as higher prevalence of CHF, prior MI, diabetes, and higher plasma concentrations of creatinine and CRP. Notwithstanding these factors, a multiple-variable linear model including age, sex, diabetes, hypertension, smoking, previous MI, CHF, and baseline concentrations of creatinine, LDL-C, HDL-C, CRP, and TnT explained less than half of the variation of suPAR concentrations. This result suggests that additional and as yet not defined mechanisms contribute to plasma suPAR concentrations. As opposed to CRP, suPAR was a highly significant predictor of adverse outcomes, which indicates that these 2 biomarkers probably reflect different aspects of the inflammatory pathology that may be manifested during follow-up of acute chest pain patients (24). The origin of suPAR in plasma is unknown, but uPAR can be found in atherosclerotic plaques (25) and is released from endothelial and inflammatory cells upon activation (26–28). In the future, it will be important to determine the underlying mechanisms for release of suPAR to the circulation and any potential pathophysiological role of suPAR.

Potential study limitations merit consideration. This study was based on blood samples obtained from a rather homogeneous white population in a single center with a limited sample size, factors which might limit the applicability of the results to other ethnic populations. Patients were admitted at the discretion of the on-call physician when NSTEACS was suspected, i.e., a heterogeneous population which, however, is likely to reflect typical acute chest pain patients in the emergency department. Moreover, the clinical parameters on which this study relied were established on the basis of information gathered from the hospital charts, which, like the timing of blood sampling, was not standardized. Variables that were available only in a minority of patients, e.g., left ventricular ejection fraction (LVEF), were not included in the models and an important biomarker such as NT-proBNP (N-terminal pro-B-type natriuretic peptide) was not measured in this cohort. Nevertheless, suPAR still predicted all-cause mortality in the 168 patients with measurements of LVEF in the fully adjusted model [HR 1.96 (95% CI, 1.22–3.14); P = 0.006]. Also, we had no information about heart rate or blood pressure at admission excluding the use of GRACE or TIMI risk scores. Furthermore, the follow-up of the study patients relied on the accuracy of the diagnoses listed in the Danish Central Civil Register, although the diagnosis of MI in this setting has been validated (29). The use of national registers for follow-up did not allow for detailed scrutiny of the causes of death. Finally, the blood samples used were part of a biobank endeavor. Although suPAR has been found to be stable in frozen blood samples (14), the samples were stored for several years before analysis, potentially leading to biomarker degradation, but this would be expected to attenuate the prognostic capability of the biomarker.

In conclusion, increased circulating concentrations of soluble urokinase plasminogen activator receptor in patients with acute chest pain and suspected NSTEACS are associated with poor prognosis and provide independent prognostic information beyond established cardiovascular risk factors. These findings require independent verification in a multicenter prospective cohort.

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References


