

Soluble urokinase plasminogen activator receptor (suPAR) is a novel, independent predictive marker of myocardial infarction in HIV-1-infected patients: a nested case-control study

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Objectives

Patients infected with HIV are at increased risk of myocardial infarction (MI). Increased plasma levels of the inflammatory biomarker soluble urokinase plasminogen activator receptor (suPAR) have been associated with increased risk of cardiovascular diseases (CVD), including MI in the general population. We tested suPAR as a predictive biomarker of MI in HIV-1-infected individuals.

Methods

suPAR levels were investigated in a nested case-control study of 55 HIV-1-infected cases with verified first-time MI and 182 HIV-1-infected controls with no known CVD. Controls were matched for age, gender, duration of antiretroviral therapy (ART), smoking and no known CVD. suPAR was measured in the four plasma samples available for each patient at different time-points; 1, Before initiation of ART; 2, 3 months after initiation of ART; 3, 1 year before the case's MI; and 4, The last sample available before the case's MI.

Results

In unadjusted conditional regression analysis, higher levels of suPAR were associated with a significant increase in risk of MI at all time-points. Patients in the third and fourth suPAR quartiles had a three- to 10-fold higher risk of MI compared to patients in the lowest suPAR quartile at all time-points. suPAR remained a strong significant predictor of MI, when adjusting for HIV-1 RNA, total cholesterol, triglycerides and high-density lipoprotein.

Conclusion

Elevated suPAR levels were associated with increased risk of MI in HIV-infected patients, suggesting that suPAR could be a useful biomarker for prediction of first-time MI in this patient group, even years before the event.

Keywords: atherosclerosis, biomarker, cardiovascular disease, inflammation, lipids

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Introduction

In countries with free access to antiretroviral therapy (ART), infection with HIV has become a chronic manageable condition, and nonAIDS comorbidities have become an increasing concern. In particular, patients infected with HIV-1 are at increased risk of cardiovascular disease (CVD) [1–3], such as myocardial infarction (MI), with an estimated 50% increased risk beyond that

explained by recognized cardiovascular risk factors [4]. HIV-accelerated chronic inflammation and immune perturbation, despite ART, might be directly associated with vascular dysfunction and the accelerated development of CVD [1,5]. However, also ART itself has been suggested as a potential factor leading to increased risk of MI through disturbances in the lipid metabolism and/or a direct effect on the cardiovascular system [6]. Biomarkers related to inflammation and associated with risk of CVD may help identify those HIV-1-infected patients with the highest risk of disease and allow early and preventive intervention. Among the more promising biomarkers are interleukin 6 (IL-6), D-dimer, C-reactive protein (CRP) [7,8], soluble tumor necrosis factor receptor (sTNFR) I and -II [9], and, as we have recently shown in a sub group of the present cohort, plasminogen activator inhibitor-1 (PAI-1) [10].

Soluble urokinase plasminogen activator receptor (suPAR) is a stable plasma biomarker associated with inflammation and immune activation. suPAR can bind urokinase plasminogen activator (uPA) and has been suggested to act as a uPA-scavenger [11,12] thereby inhibiting the catalytic process mediated by uPA with possible implications of fibrinolysis inhibition.

suPAR is a strong prognostic marker of disease severity and mortality in different patient populations [13,14], including HIV-1-infected patients [15,16]. In the general population, increased plasma suPAR levels have been associated with an increased risk of CVD, including MI [14,17,18], but it remains unknown whether suPAR is a useful marker for CVD in HIV-1-infected patients.

In this study, we aimed to investigate the potential role of suPAR as a prognostic marker of first-time MI in patients with HIV.

Materials and methods

Design and study population

In a nested case-control study previously described [19], 55 HIV-1-infected patients with verified first-time MI were compared with 182 HIV-1-infected controls with no CVD event. Briefly, data were extracted from the Danish National Patient Register on patients given a diagnosis of ischaemic heart disease and HIV [International Classification of Diseases-10th Revision (ICD10) I20-25 and B20-24] from January 1998 to December 2008. Among these, patients registered in the Danish HIV Cohort Study (DHCS) were identified, and only patients with verified first-time MI according to international criteria were included in the study. Stored

plasma samples from routine visits were analysed. Written informed consent for the storage and scientific analysis of blood samples was obtained from all participants and the study approved by the Scientific Ethical Committee of the Capital Region of Denmark (KF H-C-2008-108).

The date of the case's MI served as index date for the selection of controls from the DHCS. Up to four controls were obtained per case. Individuals with diabetes and/or CVD, other than hypertension, were excluded. All patients in the study received ART. Controls were matched with their respective case for age at the time of MI \pm 3 years, gender, duration of ART and smoking.

The study set-up included four plasma samples for each patient at four time-points: 1, Last available sample before initiation of ART; 2, 3 months after initiation of ART; 3, 1 year before the case's MI; and 4, The last sample available before the case's MI.

Plasma analysis of suPAR and blood lipids

Plasma samples were stored at -80°C until the analysis of suPAR levels, using the commercially available CE/IVD approved suPARnostic[®] ELISA (ViroGates A/S, Birkerød, Denmark) according to the manufacturer's instruction. The suPARnostic[®] ELISA has been validated to measure suPAR concentrations of 0.6–22 ng/mL. Total cholesterol, high-density lipoprotein (HDL) and triglycerides (TG) were analysed on a Vitros 5.1 Chemistry System (Ortho Clinical Diagnostics, New York, NY, USA). Very low-density lipoprotein (VLDL) was calculated by the formula $\text{TG (mmol/L)} \times 0.45$, and LDL was calculated by the formula: $\text{total cholesterol (mmol/L)} - [\text{HDL (mmol/L)} + \text{VLDL (mmol/L)}]$.

Statistical analysis

Conditional logistic regression was used to estimate odds ratios (OR) for the association of suPAR and MI and for the comparison of intergroup differences. Adjustment for co-variables was performed with multiple conditional regression analysis, and associations between all predictors and outcome were analysed for the full model. LDL and VLDL were not included in multiple conditional logistic regressions because they were calculated from the other lipids. Correlation analyses were performed on log-transformed values.

Tests for interaction were performed using a general linear model. The SPSS 20 software (IBM, Armonk, NY, USA) was used for all statistical analysis. A value of $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

The study population included 55 cases and 182 matched controls. Study participant characteristics are shown in Table 1. More than 80% of all patients had suppressed viral load (HIV-1 RNA <400 copies/mL) and CD4 cell count above 400 cells/ μ L in plasma sample 4 and did not differ in ART regimen at any time-point. The cases, however, had a tendency towards higher values of total-cholesterol, LDL and TG, and lower HDL in all samples (Table 2).

suPAR levels are significantly associated with MI at all time-points

Figure 1 shows the median plasma suPAR levels at the four time-points. Cases had significantly higher suPAR levels compared to controls at all time-points [time-point 1: 5.2 ng/mL (3.6–7.7) vs. 4.2 ng/mL (3.0–6.1); time-point 2: 4.5 ng/mL (3.4–5.3) vs. 3.6 ng/mL (2.9–4.7); time-point 3: 4.3 ng/mL (3.5–5.2) vs. 3.4 ng/mL (2.7–4.3); time-point 4: 4.4 ng/mL (3.6–5.6) vs. 3.5 ng/mL (2.8–4.6); ranges in parentheses indicate IQR, $P < 0.05$].

In an unadjusted conditional regression analysis, an increase in suPAR of 1 ng/mL was associated with an increased risk of MI by 12% (95% CI: 1–25) at time-point 1, 26% (95% CI: 3–55) at time-point 2, 29% (95% CI: 6–56) at time-point 3, and 23% (95% CI: 5–45) at time-point 4 ($P < 0.05$ for all time-points; Table 3). In a multiple conditional regression analysis, suPAR was adjusted for total cholesterol, HDL, TG, and HIV-1 RNA. The univariate and multiple analyses between all predictors and outcome are shown in Table 3.

suPAR quartiles and risk of MI

Compared with patients in the lowest (1st) suPAR quartile, the risk of MI was significantly higher in the 3rd and 4th suPAR quartiles at all time-points (Fig. 2a). Especially 1 year before MI (time-point 3), there was a pronounced increase in risk of MI for patients in the 3rd and 4th suPAR quartiles with odds ratios of 7.41 (95% CI: 2.11–26.05, $P < 0.01$) and 10.38 (95% CI: 2.82–38.27, $P < 0.001$), respectively (Fig. 2a). But even before initiation of ART (time-point 1), there was an increased risk with odds ratios of 3.17 (95% CI: 1.05–9.59, $P < 0.05$) and 4.33 (95% CI: 1.44–13.03, $P < 0.01$) for the 3rd and 4th suPAR quartiles, respectively (Fig. 2a).

Table 1 Demographic characteristics of the HIV-1-infected patients with first-time myocardial infarction and the HIV-1-infected controls

Variable	Cases	Controls	<i>P</i>
Number of patients	55	182	
Gender (male/female) (%)	50/5 (91/9)	167/15 (92/8)	0.84
Age at time of MI/index date median (IQR), years	49 (42–57)	50 (43–57)	0.77
Smoking (never/previous/current) (%)	3/8/44 (6/14/80)	7/51/123 (4/28/68)	0.12
Duration of HIV before MI/index date median (IQR), years	10 (6–17)	10 (7–16)	0.71
Blood pressure, systolic median (IQR)	135 (120–149) <i>n</i> = 36	125 (115–140) <i>n</i> = 87	0.09
Lipid-lowering treatment (%)*	6	4	0.6
Intervals between plasma samples (median (IQR), days)			
From time-point 1 to initiation of ART	42 (24–76)	49 (32–81)	
From initiation of ART to time-point 2	99 (88–123)	109 (87–142)	
From time-point 3 to MI/index date	334 (292–367)	368 (334–408)	
From time-point 4 to MI/index date	52 (27–82)	0 (0–0)	

ART, antiretroviral therapy; IQR, interquartile range; MI, myocardial infarction.

*Within the study period.

suPAR levels predict MI independently of HIV-1 RNA and blood lipids

In a multiple conditional logistic regression analysis of suPAR quartiles adjusting for HIV-1 RNA, total cholesterol, HDL, and triglycerides, suPAR remained an independent predictor of MI. At time-point 3, risk of MI remained strongly associated with high suPAR with odds ratios of 7.18 (95% CI: 1.97–26.24, $P < 0.01$) and 9.09 (95% CI: 2.37–34.87, $P < 0.01$) for patients in the 3rd and 4th suPAR quartiles, respectively, compared to patients in the lowest suPAR quartile (Fig. 2b). Furthermore, the 4th suPAR quartile at time-point 1 (before ART) and time-point 2 (3 months after ART) were also associated with an increased risk of MI [OR (95% CI): 7.94 (1.35–46.79), $P < 0.05$, and OR (95% CI): 4.76 (1.41–16.10), $P = 0.01$] (Fig. 2b).

In the multiple analyses, total cholesterol was significantly associated with MI at time-point 1 [OR (95% CI): 1.72 (1.07–2.76), $P < 0.05$], time-point 2 [OR (95% CI): 1.65 (1.15–2.38), $P < 0.01$], and time-point 4 [OR (95%

Table 2 Characteristics of the study groups at the four sample time-points: 1, the last sample available before initiation of ART; 2, 3 months after initiation of ART; 3, 1 year before the case's MI/index date; and 4, the last sample available before the case's MI/index date

	Sample 1			Sample 2			Sample 3			Sample 4		
	Cases	Controls	P	Cases	Controls	P	Cases	Controls	P	Cases	Controls	P
CD4 count, cells/ μ L, median (IQR)	170 (81–235)	199 (84–296)	0.13	256 (186–383)	271 (150–377)	0.73	433 (279–660)	500 (310–730)	0.32	496 (290–688)	547 (307–800)	0.78
HIV-1 RNA copies/mL, median (IQR)	114 808 (33 150–271 750)	51 257 (13 109–166 598)	0.27	199 (28–399)	199 (20–399)	0.66	39 (19–1590)	38 (19–43)	0.12	39 (19–92)	39 (19–40)	0.08
Total cholesterol mmol/L, median (IQR)	4.8 (3.9–5.1)	4.2 (3.5–4.9)	0.04	5.4 (4.4–6.5)	4.8 (4.1–5.8)	0.03	5.1 (4.2–6.6)	5.1 (4.4–6.0)	0.41	5.6 (4.6–6.3)	5.2 (4.4–6.0)	0.05
LDL mmol/L, median (IQR)	3.0 (2.1–3.6)	2.5 (1.9–3.2)	0.04	3.1 (2.3–4.6)	2.9 (2.1–3.6)	0.06	3.1 (2.1–4.6)	3.0 (2.3–3.8)	0.40	3.4 (2.4–4.2)	3.0 (2.3–3.8)	0.04
Triglycerides mmol/L, median (IQR)	1.9 (1.4–2.9)	1.7 (1.2–2.3)	0.06	2.3 (1.8–3.2)	2.1 (1.3–2.9)	0.05	2.6 (1.9–3.1)	2.1 (1.4–2.9)	0.14	2.4 (1.7–3.5)	2.2 (1.3–3.1)	0.09
HDL mmol/L, median (IQR)	0.72 (0.7–0.9)	0.78 (0.6–0.9)	0.12	0.9 (0.7–1.0)	1.0 (0.8–1.2)	0.15	0.9 (0.7–1.1)	1.1 (0.9–1.3)	0.03	0.9 (0.8–1.2)	1.0 (0.8–1.3)	0.08
NRTI (%)	NA	NA	NA	100	98	0.49	98	98	0.91	96	98	0.39
PI (%)	NA	NA	NA	81	77	0.23	62	58	0.62	56	56	0.93
NNRTI (%)	NA	NA	NA	15	21	0.12	46	41	0.37	46	45	0.73
Other ART	NA	NA	NA	0	0	NA	0	0	NA	2	1	0.33

P-values are calculated with conditional logistic regression. ART, antiretroviral therapy; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; NNRTI, non-nucleoside reverse-transcriptase inhibitors; NRTI, nucleoside reverse-transcriptase inhibitors; PI, protease inhibitors.

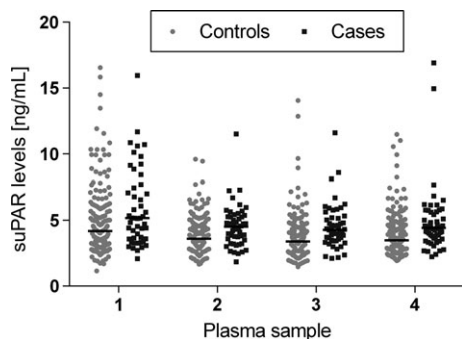


Fig. 1 Scatter plot of plasma suPAR levels (ng/mL) for controls (circles) and cases (squares) at four different time-points: 1, the last sample available before initiation of ART; 2, 3 months after initiation of ART; 3, 1 year before the case's MI/index date; and 4, the last sample available before the case's MI/index date. Horizontal lines indicate medians. $P < 0.05$ for all samples. ART, antiretroviral therapy; MI, myocardial infarction; suPAR, soluble urokinase plasminogen activator receptor.

CI): 1.45 (1.12–1.89), $P < 0.01$). At time-point 3 the association was borderline significant [OR (95% CI): 1.28 (0.95–1.71), $P = 0.11$].

Correlations between suPAR and markers of HIV infection and PAI-1

suPAR was significantly correlated with HIV-1 RNA except at time-point 2 (time-point 1: $r = 0.16$, $P = 0.04$; time-point 2: $r = 0.06$, $P = 0.38$; time-point 3: $r = 0.20$, $P = 0.003$; time-point 4: $r = 0.16$, $P = 0.02$). An inverse, significant correlation was found between suPAR and CD4 cell count except at time-point 2, where the correlation was border-line significant (time-point 1: $r = -0.28$, $P < 0.0001$; time-point 2: $r = -0.14$, $P = 0.052$; time-point 3, $r = -0.21$, $P = 0.002$; time-point 4, $r = -0.20$, $P = 0.003$).

We have previously published data on PAI-1 and the risk of MI at time-points 3 and 4 in a sub-group of this sample [10] and we therefore performed a correlation analysis of suPAR and PAI-1 at time-points 3 and 4, but no correlation was found (data not shown). No interaction was found between case-control status and the correlated parameters.

Discussion

In this case-control study, we show for the first time that suPAR is a strong independent predictor of MI among HIV-1-infected patients. Elevated suPAR levels were strongly and significantly associated with subsequent development of first-time MI, even years before the event. The association persisted after adjustment for HIV-1 viral load and blood lipids.

Inflammatory biomarkers such as CRP, D-dimer and IL-6 have all been suggested to predict cardiovascular events in HIV-1-infected patients, even with full viral suppression obtained by ART [7–9]. However, it remains debated whether the ART itself is involved in the development of MI among HIV-1-infected patients [1,6]. Our findings seem to suggest that ART did not play a direct role in the development of MI, given that suPAR levels among cases were already increased before initiation of ART. This indicates that the cases had an inherent risk of CVD unrelated to their HIV treatment or, in other words, that suPAR predicts MI through pathways independent of ART use.

suPAR has previously been shown to predict mortality in treatment-naïve HIV-1-infected patients [16]. In HIV-patients initiating ART, mortality was concentrated in the highest suPAR quartile, while patients with a low suPAR level had a low risk of mortality despite low CD4 cell count and low body weight [15]. Thus, suPAR appears to add significant information to other measures of poor prognosis in HIV-infected patients.

Table 3 Univariate and multiple conditional logistic regression analysis for myocardial infarction at four samples taken at different time-points: 1, the last sample available before initiation of ART; 2, 3 months after initiation of ART; 3, 1 year before the case's MI/index date; and 4, the last sample available before the case's MI/index date

	Sample 1		Sample 2		Sample 3		Sample 4	
	Univariate	Multiple	Univariate	Multiple	Univariate	Multiple	Univariate	Multivariate Multiple
suPAR	1.12 (1.01–1.25)	1.13 (0.95–1.34)	1.26 (1.03–1.55)	1.27 (1.01–1.61)	1.29 (1.06–1.56)	1.24 (1.01–1.52)	1.23 (1.05–1.45)	1.33 (1.09–1.63)
Total cholesterol	1.41 (1.02–1.94)	1.72 (1.07–2.76)	1.36 (1.04–1.78)	1.65 (1.15–2.38)	1.11 (0.87–1.41)	1.28 (0.95–1.71)	1.24 (1.00–1.53)	1.45 (1.12–1.89)
HDL	0.37 (0.11–1.27)	0.30 (0.02–5.16)	0.45 (0.15–1.35)	0.36 (0.07–1.89)	0.31 (0.11–0.90)	0.34 (0.09–1.27)	0.44 (0.18–1.09)	0.42 (0.12–1.49)
Triglycerides	1.46 (0.99–2.16)	1.49 (0.78–2.88)	1.38 (0.99–1.92)	1.35 (0.89–2.06)	1.21 (0.94–1.56)	1.01 (0.76–1.35)	1.25 (0.97–1.62)	1.08 (0.78–1.49)
log(HIV-1 RNA)	1.53 (1.02–2.28)	1.62 (1.04–2.52)	0.99 (0.68–1.48)	0.96 (0.63–1.47)	1.39 (1.06–1.82)	1.33 (1.00–1.76)	1.36 (0.96–1.91)	1.32 (0.91–1.91)

Numbers shown are odds ratios (95% confidence intervals).

HDL, high-density lipoprotein; suPAR, soluble urokinase plasminogen activator receptor.

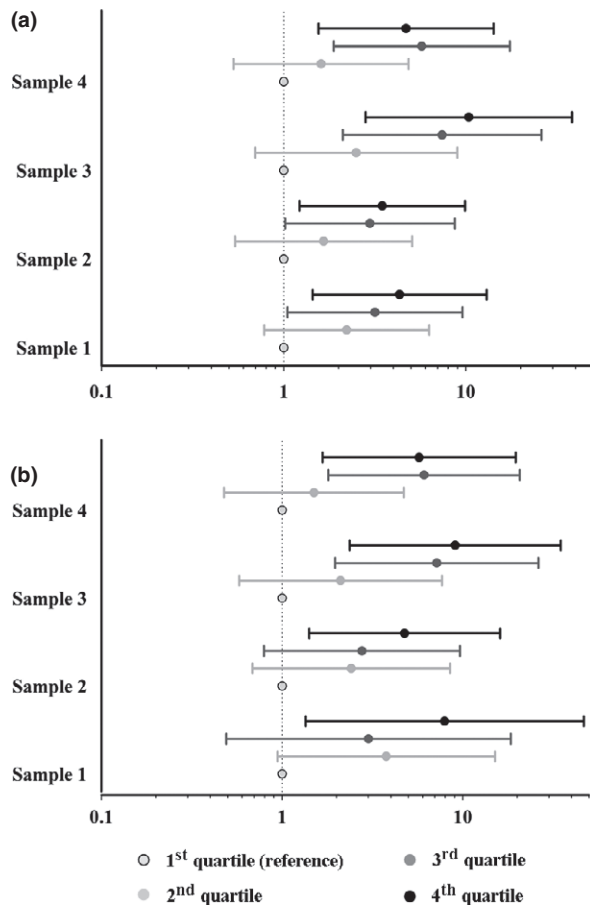


Fig. 2 The risk of myocardial infarction (odds ratios, 95% CI) for patients with plasma suPAR levels in the upper three quartiles compared to the lowest quartile at four different time-points: 1, the last sample available before initiation of ART; 2, 3 months after initiation of ART; 3, 1 year before the case's MI/index date; and 4, the last sample available before the case's MI/index date. (a) Unadjusted and (b) adjusted for HIV-1 viral load, total cholesterol, HDL and triglycerides. ART, antiretroviral therapy; CI, confidence interval; HDL, high-density lipoprotein; MI, myocardial infarction; suPAR, soluble urokinase plasminogen activator receptor.

We found that suPAR levels were lower in both cases and controls at the sampling points after initiation of ART therapy, which correlates well with previous findings [20,21]. suPAR has been suggested to be a marker of metabolic disturbances, such as lipodystrophy, dyslipidemia and insulin resistance, in HIV-infected patients [22,23], which are all potential cofactors in the pathogenesis of MI among HIV-infected patients, but in this study suPAR predicted MI independently of lipid values. Together, these findings suggest that beside the risk associated with the traditional risk factors, such as total cholesterol and LDL, suPAR may reflect a different pathogenesis of a more inflammatory nature.

PAI-1 has previously been associated with MI in a subgroup of this cohort [10], and as suPAR can act as a uPA-scavenger our findings in this study cohort could point to a theory of hypercoagulability in the development of MI in HIV-1-infected patients, even with full viral suppression. However, we found no correlation between PAI-1 and suPAR in a sub-population of this cohort. The contribution of a hypercoagulable state to morbidity and mortality in HIV has been observed in other studies, showing that D-dimer is associated with CVD and mortality in HIV-1-infected patients [7,9,24].

The present results introduce suPAR as a potential novel inflammatory marker of cardiovascular events in HIV-infected patients with a > 10-fold increase in risk of MI for patients with the highest suPAR levels. The use of suPAR as an indicator/surrogate marker for the chronic inflammation associated with increased cardiovascular risk and other nonAIDS-related morbidities may markedly improve the risk stratification of routinely followed HIV-patients and may aid in the identification of those patients mostly at risk of CVD events beyond the information provided by traditional risk factors; a property of suPAR, which is also observed in the general population [17,18]. Intriguingly, suPAR predicted the cardiovascular events even before the initiation of ART and may therefore be of guidance in both the choice of ART and direct focus towards early signs of co-morbidities in this population at risk.

The study has some limitations. The case-control design is associated with the risk of selection bias and residual confounding, and furthermore, the number of cases in the study was low. We have no information on tobacco use or smoking intensity on an individual basis. Therefore, we cannot exclude the possibility that cases had higher intensity of smoking, which has been found to correlate with suPAR levels [25]. Furthermore, it is important to underline that there is a higher percentage of previous smokers among the controls, causing a slight skewness of the data. Another limitation to this study is the lack of measurements of other competent inflammatory markers, such as IL-6 and TNF receptors, which has recently been shown to be associated with nonAIDS-defining events [9]. However, suPAR has previously been shown to be positively correlated with sTNFR-II and IL-6 in HIV-1-infected individuals [21,22], suggesting that these inflammatory markers reflect similar aspects of HIV-associated inflammation. As PAI-1 was only analysed in a subgroup of the cohort, it is not possible to adjust for PAI-1 in the full model. All of the necessary parameters for the creation of an individual cardiovascular risk score, such as the Framingham risk score, were

not registered, and we are therefore unable to test if the addition of suPAR to an existing risk score could increase the AUC.

Conclusion

In conclusion, this nested case-control study of 55 cases and 182 controls showed that elevated plasma suPAR levels were independently associated with an increased risk of developing first-time MI in an HIV-1-infected population. Thus, suPAR may be a new risk marker in the monitoring and management of comorbidities among HIV-1-infected patients even years before the event.

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Conflicts of interest: JEO is a founder, shareholder, and board member of ViroGates A/S, Denmark, the company that produces the suPARnostic® assay. JEO is also an inventor on a patent on suPAR and risk. Copenhagen University Hospital Hvidovre, Denmark, owns the patent, which is licensed to ViroGates A/S.

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