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ORIGINAL RESEARCH

Proteomics-Based Soluble Urokinase Plasminogen Activator Receptor Levels Are Associated With Incident Heart Failure Risk

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ABSTRACT

BACKGROUND Higher soluble urokinase plasminogen activator receptor (suPAR) levels are associated with adverse outcomes in chronic heart failure (HF).

OBJECTIVES The authors assessed the association between proteomics-based suPAR levels and incident HF risk in the general population.

METHODS In 40,418 UK Biobank participants without HF or coronary artery disease at enrollment, the association between Olink-based suPAR levels measured as relative protein expression levels and incident all-cause, ischemic, and nonischemic HF was analyzed by competing-risk regression, while accounting for all-cause death as a competing risk. The additional variability in incident HF risk attributable to suPAR levels beyond demographics, traditional risk factors, N-terminal pro B-type natriuretic peptide (NT-proBNP), and C-reactive protein (CRP) levels was assessed with nested Cox modeling and likelihood ratio testing.

RESULTS The mean age was 56 years; 45% were male, and 94% were White. During a median follow-up of 13.7 (IQR: 1.5) years, 1,428 (3.5%) incident HF events occurred. Proteomics-based suPAR levels (per 1-SD) were independently associated with incident HF (subdistribution HR (sHR): 1.37, 95% CI: 1.29-1.46), ischemic HF (sHR: 1.40, 95% CI: 1.28-1.54), and nonischemic HF (sHR: 1.32, 95% CI: 1.21-1.44) risk, after adjustment for demographics, traditional cardiovascular risk factors, NT-proBNP, and CRP levels. The addition of suPAR levels to a base risk factor model significantly improved the explained variability of incident HF risk ($R^2 = 0.76$ vs 0.73, $P < 0.001$).

CONCLUSIONS Independent of demographics, traditional risk factors, NT-proBNP, and CRP levels, proteomics-based suPAR levels were significantly associated with incident all-cause, ischemic, and nonischemic HF risk. Proteomics-based measurement of suPAR levels may underestimate the effect size of this relationship. (JACC Adv. 2025;4:101442) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

BNP = B-type natriuretic peptide

CAD = coronary artery disease

CRP = C-reactive protein

eGFR = estimated glomerular filtration rate

HDL-C = high-density lipoprotein cholesterol

LV = left ventricle

MI = myocardial infarction

NT-proBNP = N-terminal pro B-type natriuretic peptide

sHR = subdistribution HR

suPAR = soluble urokinase plasminogen activator receptor

UKB-PPP = UK Biobank Pharma Proteomics Project

uPAR = urokinase plasminogen activator receptor

Heart failure is a complex clinical syndrome with significant morbidity and mortality.[1] Among older American adults, heart failure prevalence is approximately 4.3% and is expected to rise to 8.5% by 2030.[2,3] Despite improvement in heart failure treatment in recent decades, rates of heart failure hospitalizations have increased.[4,5] Thus, preventive strategies are critical in mitigating the global burden of heart failure, and an individualized approach to heart failure risk prediction and prevention is needed.

A multitude of distinct biological phenomena contribute to the development of heart failure, and various biomarkers have been linked to these underlying mechanisms.[6] Soluble urokinase plasminogen activator receptor (suPAR) is the circulating form of the *PLAUR* gene product urokinase plasminogen activator receptor and is released into the bloodstream during inflammation, immune activation, and endothelial dysfunction. Elevated suPAR levels have been shown to be a pathogenic risk factor for kidney disease and atherosclerosis, and given the role of renal dysfunction and coronary artery disease in heart failure pathogenesis, suPAR is uniquely positioned for examination as a contributor to incident HF risk.[7,8] Accordingly, recent studies have implicated elevated suPAR levels with heart failure severity.[9,10] The role that suPAR might play in its association with incident heart failure in healthy individuals is, however, less established and has not been evaluated in a large general population sample independently of other predictive biomarkers and across differing heart failure severity or subtypes.

Herein, we examined the relationship between circulating suPAR levels estimated by the Olink proteomics platform and incident heart failure risk in a healthy population, with the hypothesis that proteomics-based suPAR levels would be associated with incident heart failure and heart failure subtypes, independent of the established predictive biomarkers N-terminal pro B-type natriuretic peptide (NT-proBNP) and C-reactive protein (CRP).[5,11] Given that suPAR levels are known to be higher in women compared to men, we additionally examined the association of suPAR levels and incident heart failure risk in sex-specific analyses.[12] suPAR levels measured by the Olink proteomics platform correlate modestly to gold-standard, immunoassay methods of suPAR measurement and also appear to underestimate the ability of suPAR to discriminate the risk of important outcomes, such as all-cause and cardiovascular mortality.[13] As such, it is important to interpret results from Olink-based suPAR levels within this context.

METHODS

STUDY POPULATION. The United Kingdom Biobank (UK Biobank) is a population-based, prospective cohort study of approximately 500,000 participants from across the United Kingdom who were aged 40 to 69 years during the recruitment period of 2006 to 2010.[14] The recruitment criteria for the UK Biobank have been described previously.[15]

The current study included UK Biobank participants without heart failure at the time of enrollment, with heart failure being defined as International Statistical Classification of Diseases and Related Health Problems-10th Revision (ICD-10) code I50. Participants with a history of coronary artery disease (CAD) at the time of UK Biobank enrollment were also excluded, with CAD being defined as any prior occurrence of angina pectoris, acute myocardial infarction (MI), subsequent MI, complications following MI, other acute ischemic heart disease, or chronic ischemic heart disease (I20-I25). Participant-level, Olink-based proteomics data collected at the time of recruitment included suPAR, as the circulating gene product of *PLAUR*, and NT-proBNP and was available in a sub-sample of approximately 50,000 UK Biobank participants through the UK Biobank Pharma Proteomics Project (UKB-PPP).[16] Only participants from this sub-sample of the UK Biobank without missing covariate data were included in our analysis, resulting in a study sample without heart failure or CAD and with proteomics-based suPAR and NT-proBNP data available (Supplemental Figure 1).

Clinical information related to demographics (age, sex, and ethnicity) and traditional cardiovascular risk factors (body mass index [BMI], smoking history, diabetes mellitus, hypertension, total cholesterol, high-density lipoprotein cholesterol [HDL-C], estimated glomerular filtration rate [eGFR] calculated using the 2021 CKD-EPI equation, blood pressure medication usage, and cholesterol medication usage) was obtained from enrollment data.[17] Proteomics-based suPAR and NT-proBNP levels were obtained from UKB-PPP data, and CRP levels were obtained by direct measurement.

The UK Biobank has received approval from the North West Multicentre Research Ethics Committee and holds current approval as a Research Tissue Bank, such that researchers do not require separate ethical clearance.

MEASUREMENT AND NORMALIZATION OF BIOMARKER LEVELS. Venous blood was collected at participants' baseline visits and stored in a −80 °C freezer prior to processing. Analysis of proteomics-based suPAR and NT-proBNP levels in UKB-PPP participants was performed with Olink technology utilizing the Proximity Extension Assay. Normalized protein expression levels were then calculated utilizing individual participants' gene product levels, resulting in suPAR and NT-proBNP levels described as values relative to other UKB-PPP participants. These processes have been described in detail elsewhere.[18,19]

Rank-based inverse normal transformation of suPAR and NT-proBNP levels was performed to achieve data normalization and to allow for examination per change in 1 SD. As CRP levels were directly measured, CRP was scaled by 1 SD to also allow for examination per change in 1 SD.

FOLLOW-UP AND OUTCOMES. UK Biobank data were linked to primary care data and Hospital Episode Statistics data, which include all hospital admissions until September 2023 dating back to 1997 for England, 1998 for Wales, and 1981 for Scotland. ICD-10 codes were utilized to designate the occurrence of heart failure, CAD, diabetes mellitus, and hypertension. Death registries utilized included all deaths until September 2023.

The primary outcome was defined as the diagnosis of incident heart failure in either the inpatient or outpatient setting. Secondary outcomes analyzed included the diagnosis of incident ischemic heart failure and diagnosis of incident nonischemic heart failure. Incident ischemic heart failure was defined in participants with a diagnosis of CAD prior to or up to 1 year following the diagnosis of incident heart failure to allow time for the scheduling and performance of diagnostic measures for CAD. Incident nonischemic heart failure was defined in cases of incident heart failure wherein the definition for ischemic heart failure was not satisfied.

Follow-up time was defined as the time from enrollment until incident heart failure diagnosis, all-cause mortality, end of follow-up, or loss to follow-up.

STATISTICAL ANALYSES. Descriptive statistics. Baseline characteristics were reported as descriptive statistics with absolute counts (percentages) for categorical variables and mean ± SD for continuous variables. Correlations between biomarker levels were assessed by Pearson correlation.

Survival analyses. Proteomics-based suPAR levels were examined as a continuous variable per change in one SD. We first examined suPAR levels by quintile in a Kaplan–Meier survival analysis to visualize the association between suPAR levels and incident all-cause heart failure. We then utilized stepwise Fine and Gray competing-risk regression models to examine the independent association between suPAR levels and incident heart failure risk, while accounting for all-cause mortality.[20] Model 1 included suPAR. Model 2 included suPAR and demographics (age, sex, and race [White versus non-White]). Model 3 included demographics and traditional risk factors (BMI, smoking history, diabetes mellitus, hypertension, total cholesterol, HDL-C, eGFR, blood pressure medication use, and cholesterol medication use). Model 4 included demographics, traditional risk factors, and NT-proBNP. Model 5 added CRP to Model 4. suPAR was additionally examined by quintile in a competing-risk regression model to compare the risk of incident heart failure in individuals in the highest quintile of suPAR levels to those in the lowest quintile of suPAR levels. We also examined the relationship between high and low suPAR and NT-proBNP levels (according to sample median of each biomarker) with incident all-cause heart failure by Kaplan–Meier survival and multivariable-adjusted competing-risk regression analyses.

A sensitivity analysis was performed to explore for heterogeneity of associations between proteomics-based suPAR and other factors significantly associated with incident heart failure risk discovered in Model 5. Individual multiplicative interaction analyses were performed in competing-risk regression models for incident heart failure, while accounting for all-cause death. To perform these analyses, age was dichotomized at 65 years, BMI at 30 kg/m^2, eGFR at 90 mL/min/1.73 m^2, NT-proBNP at the median, and CRP at the median. Posthoc construction of sex-specific splines with the R package smoothHR was performed to examine the distribution of incident heart failure risk across suPAR levels in men and women separately.[21] The sex-specific median of suPAR was utilized as the reference value, and the

TABLE 1 Baseline Characteristics of Study Population (N = 40,418)

Age (y)	56.4 ± 8.2
Male	18,120 (45%)
White race	37,974 (94%)
Body mass index (kg/m^2)	27.3 ± 4.8
Smoking history	17,983 (44%)
Diabetes mellitus	1,888 (4.7%)
Hypertension	10,277 (25%)
Total cholesterol (mg/dL)	221.4 ± 43.8
High-density lipoprotein (mg/dL)	56.4 ± 14.8
eGFR[a] (mL/min/1.73 m^2)	94.6 ± 13.6
Blood pressure medication use	7,712 (19%)
Cholesterol medication use	5,893 (15%)
CRP (mg/L)	2.6 ± 4.3
suPAR[a]	0.0 ± 1.0
NT-proBNP[a]	0.0 ± 1.0
Incident heart failure	
Incident heart failure	1,428 (3.5%)
Incident Ischemic heart failure	663 (1.6%)
Incident nonischemic heart failure	765 (1.9%)
All-cause death	3,198 (7.9%)

Values are mean ± SD or n (%). Table depicting the baseline characteristics of the study sample. [a]Values for suPAR and NT-proBNP represent Olink-based protein expression levels that have been rank-based inverse normal transformed and thus indicate values relative to other study participants per change in 1-SD.

CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro B-type natriuretic peptide; suPAR = soluble urokinase plasminogen activator receptor.

95% CI was included along the continuous spectrum of suPAR levels.

We also examined the independent association of proteomics-based suPAR levels with incident ischemic heart failure and incident nonischemic heart failure risk. For the examination of the association between suPAR and incident ischemic heart failure risk, a multivariable competing-risk regression model adjusted for demographics, traditional risk factors, NT-proBNP, and CRP levels was utilized and included both incident nonischemic heart failure and all-cause mortality as competing risks. Analysis of the association between suPAR and incident nonischemic heart failure risk was conducted similarly, except with incident ischemic heart failure and all-cause mortality included as competing risks.

Explained variance and model fit. We furthermore examined the additional variance in incident HF risk attributable to directly measured CRP levels and proteomics-based suPAR levels by constructing nested Cox models. The estimation of the proportion of variance in incident HF risk explained by each Cox model was quantified with the R^2 value, using the CoxR2 R package.[22] Likelihood ratio testing was utilized to compare nested models.

All analyses were performed with R 4.2.2. P values <0.05 were considered significant.

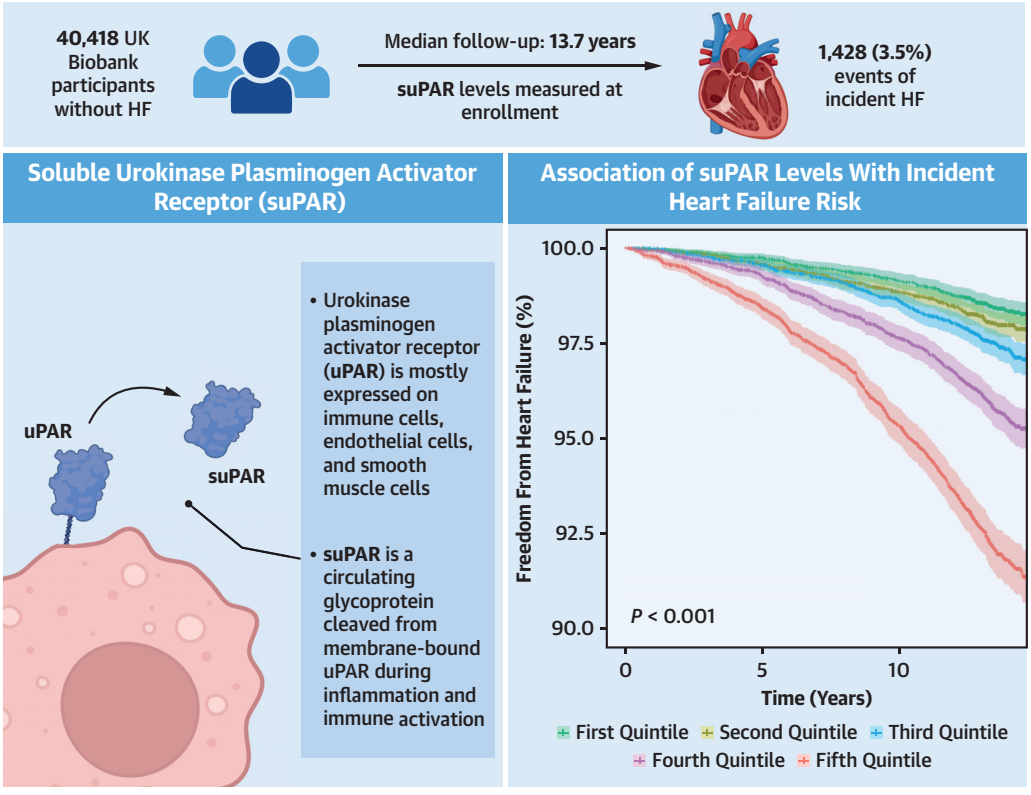
RESULTS

SAMPLE CHARACTERISTICS. The baseline characteristics of the 40,418 participants are shown in Table 1. The mean age was 56.4 ± 8.2 years; 45% were male, and 94% were of White ethnicity. Modest positive correlations were noted between proteomics-based suPAR and NT-proBNP levels (r = 0.23, $P < 0.001$), as well as between suPAR and CRP levels (r = 0.23, $P < 0.001$). A negligible albeit significant correlation was observed between NT-proBNP and CRP levels (r = 0.03, $P < 0.001$).

INCIDENT HEART FAILURE RISK. During a median follow-up of 13.7 years [IQR: 1.5 years], 1,428 (3.5%) events of incident heart failure were observed. Kaplan-Meier survival analysis examining the association between proteomics-based suPAR levels and incident heart failure risk demonstrated a significant difference in risk by suPAR quintile (log-rank $P < 0.001$) (Central Illustration). In an unadjusted competing-risk regression model accounting for all-cause mortality, suPAR levels (per 1-SD) were associated with incident heart failure risk (subdistribution HR [sHR]: 1.88, 95% CI: 1.78-1.99). Attenuation in this association was noted after adjustment for demographics and traditional cardiovascular risk factors (sHR: 1.54, 95% CI: 1.44-1.64). suPAR levels remained independently associated with incident heart failure risk even after the addition of NT-proBNP levels to the model (sHR: 1.42, 95% CI: 1.33-1.51). The serial addition of CRP levels had minimal effect on the association between suPAR levels and incident heart failure risk (sHR: 1.37, 95% CI: 1.29-1.46) (Table 2). When examined by comparison of the highest quintile of suPAR levels (N = 8,087) to the lowest quintile of suPAR levels (N = 8,083), suPAR levels were strongly associated incident heart failure risk, independent of demographics, traditional risk factors, NT-proBNP, and CRP levels (sHR: 1.88, 95% CI: 1.53-2.31).

In sensitivity analyses investigating for heterogeneity of associations between proteomics-based suPAR levels and other factors independently associated with incident HF risk discovered in the fully adjusted multivariable model, a significant interaction was identified between suPAR levels and sex in a multivariable-adjusted competing-risk regression model (P-interaction = 0.039). suPAR levels were associated with a nominally increased risk of incident heart failure in women (sHR: 1.40, 95% CI: 1.26-1.56) when compared to men (sHR: 1.36, 95% CI: 1.26-1.47)

CENTRAL ILLUSTRATION **Proteomics-Based suPAR Levels and Incident Heart Failure Risk**



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The bottom left panel shows a schematic description of suPAR. suPAR is cleaved from membrane-bound uPAR into the circulation during inflammation and immune activation. The bottom right panel depicts Kaplan-Meier curves demonstrating the significant association of proteomics-based suPAR levels by quintile with incident heart failure risk. Participants in the lowest quintile of suPAR levels (green) possess the lowest risk of incident heart failure, whereas those in the highest quintile of suPAR levels (red) possess the highest risk of incident heart failure. suPAR = soluble urokinase plasminogen activator receptor. uPAR = urokinase plasminogen activator receptor.

(Figure 1). Given this minimal difference in risk estimates, sex-specific splines were constructed to more closely examine the distribution of incident heart failure risk across suPAR levels between sexes. Whereas a linear association between suPAR levels and incident heart failure risk was observed in men, a J-shaped curve with a comparatively higher risk of heart failure at lower and higher suPAR levels was observed in women (Figure 2). The association between suPAR levels and incident heart failure risk was otherwise consistent across the remaining clinically relevant subgroups, such as age, eGFR, NT-proBNP, and CRP.

ASSOCIATION WITH INCIDENT HEART FAILURE RISK BY suPAR AND NT-proBNP LEVELS. Noting that both proteomics-based suPAR and NT-proBNP levels were independently associated with incident heart failure in multivariable regression modeling (Supplemental Table 1), we examined the relationship between these 2 biomarkers and incident heart failure risk with Kaplan-Meier survival analysis by dividing participants into high and low suPAR and NT-proBNP groups by each respective biomarkers' sample median (Figure 3). Further analysis in multivariable-adjusted competing-risk regression modeling revealed that, when compared to participants with low suPAR and low NT-proBNP levels, those with high suPAR and high NT-proBNP levels had a substantially greater risk of incident heart failure (sHR: 3.06, 95% CI: 2.55-3.68). Elevated NT-proBNP levels in the setting of low suPAR levels resulted in a comparatively poorer association with incident heart failure risk (sHR: 1.97, 95% CI: 1.61-2.42), as did elevated suPAR levels in the setting of low NT-proBNP levels (sHR: 1.47, 95% CI:

TABLE 2 Multivariable Competing-Risk Modeling of Proteomics-Based suPAR and Incident All-Cause, Ischemic, and Nonischemic Heart Failure Risk

	Incident All-Cause Heart Failure	Incident Ischemic Heart Failure	Incident Nonischemic Heart Failure
	sHR per 1-SD (95% CI)[c]	sHR per 1-SD (95% CI)[c]	sHR per 1-SD (95% CI)[c]
Model 1: suPAR	1.88 (1.78-1.99)	1.90 (1.76-2.06)	1.83 (1.70-1.97)
Model 2: suPAR, demographics[a]	1.72 (1.62-1.82)	1.66 (1.52-1.82)	1.65 (1.52-1.79)
Model 3: suPAR, demographics,[a] and traditional risk factors[b]	1.54 (1.44-1.64)	1.55 (1.41-1.69)	1.49 (1.37-1.63)
Model 4: Model 3 + NT-proBNP	1.42 (1.33-1.51)	1.44 (1.31-1.58)	1.37 (1.25-1.49)
Model 5: Model 3 + NT-proBNP + C-reactive protein	1.37 (1.29-1.46)	1.40 (1.28-1.54)	1.32 (1.21-1.44)

suPAR levels remained significantly associated with all-cause, ischemic, and nonischemic heart failure risk even after adjustment for demographics, traditional risk factors, NT-proBNP levels, and CRP levels. [a]Demographics include age, sex, and race (White versus non-White). [b]Traditional risk factors include body mass index, smoking history, diabetes mellitus, hypertension, total cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate, blood pressure medication use, and cholesterol medication use. [c]All P <0.001.

CI = confidence interval; NT-proBNP = N-terminal pro B-type natriuretic peptide; SD = standard deviation; sHR = subdistribution hazard ratio; suPAR = soluble urokinase plasminogen activator receptor.

1.20-1.81), when compared to those with low suPAR and low NT-proBNP levels.

INCIDENT ISCHEMIC AND NONISCHEMIC HEART FAILURE RISK. Over a median follow-up of 13.7 years (IQR: 1.5 years), a total of 663 (1.6%) events of incident ischemic heart failure and 765 (1.9%) events of incident nonischemic heart failure occurred. Kaplan-Meier survival analyses demonstrated a significant association between proteomics-based suPAR levels by quintile and incident ischemic (Supplemental Figure 2A) and nonischemic (Supplemental Figure 2B) heart failure risk. In competing-risk regression modeling adjusted for demographics, traditional risk factors, NT-proBNP, and CRP levels, elevated suPAR levels were independently associated with ischemic heart failure risk (sHR: 1.40, 95% CI: 1.28-1.54) with both all-cause mortality and incident nonischemic heart failure included as competing risks. Elevated suPAR levels were also independently associated with nonischemic heart failure risk (sHR: 1.32, 95% CI: 1.21-1.44) with all-cause mortality and incident ischemic heart failure included as competing risks (Table 2).

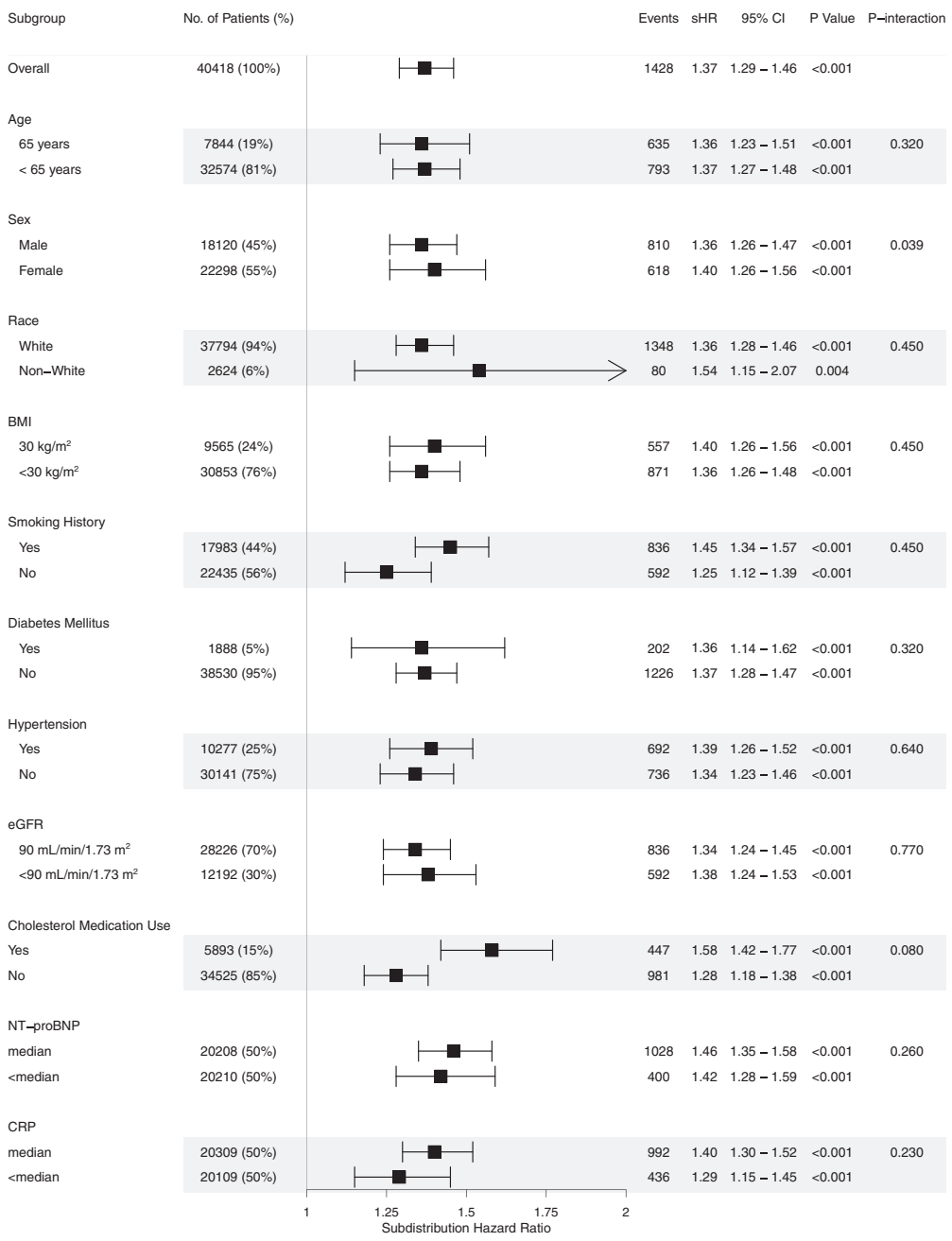
EXPLAINED VARIANCE AND MODEL FIT. The Cox proportional hazards model that included demographics, traditional risk factors, NT-proBNP, and CRP levels demonstrated an R^2 of 0.73 ($P < 0.001$). The addition of suPAR to this model resulted in an R-squared of 0.76 ($P < 0.001$), indicating a substantial increase in the explained variability of incident HF risk when compared to the base model. Likelihood ratio testing comparing these 2 nested Cox models confirmed that suPAR levels significantly improved the model's ability to explain incident HF risk ($P < 0.001$).

Regarding the relationship between CRP and proteomics-based suPAR levels with incident heart failure risk, the addition of CRP levels to a Cox model that included suPAR levels, demographics, traditional risk factors, and NT-proBNP levels did significantly explain additional variability of incident HF risk but to a lesser degree (R^2 0.76 vs 0.75, $P < 0.001$) than suPAR levels. Furthermore when compared to a model that included demographics, traditional risk factors, and NT-proBNP levels, the sole addition of suPAR levels to this model (R^2 0.75 vs 0.72, $P < 0.001$) explained the variability of incident HF risk to a greater degree the sole addition of CRP levels (R^2 0.73 vs 0.72, $P < 0.001$).

DISCUSSION

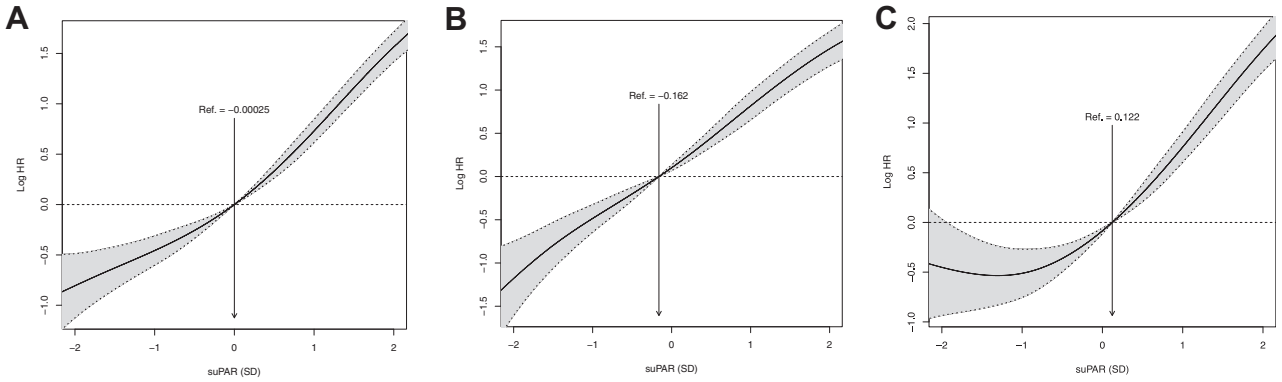
In this large, prospective cohort of initially healthy participants in the UK Biobank, we show that elevated plasma proteomics-based suPAR levels were significantly associated with new-onset ischemic and nonischemic heart failure, independent of demographics, traditional risk factors, NT-proBNP levels, and CRP levels. Participants in the highest quintile of suPAR levels had a nearly 90% higher risk per SD of developing incident heart failure compared to those in the lowest quintile of suPAR levels, and participants with elevated suPAR and NT-proBNP

FIGURE 1 **Interaction Analyses of Proteomics-Based suPAR Levels and Incident Heart Failure Risk by Subgroup**



Factors independently associated with incident heart failure risk discovered in multivariable regression modeling were included in multiplicative interaction analyses to explore for heterogeneity of associations between proteomics-based suPAR levels and incident heart failure risk. A significant interaction was observed between suPAR and sex, such that female sex was associated with a nominally higher risk of incident heart failure than male sex. BMI = body mass index; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro B-type natriuretic peptide;. suPAR = soluble urokinase plasminogen activator receptor.

FIGURE 2 Sex-Specific Distribution of Incident Heart Failure Risk Across Proteomics-Based suPAR Levels



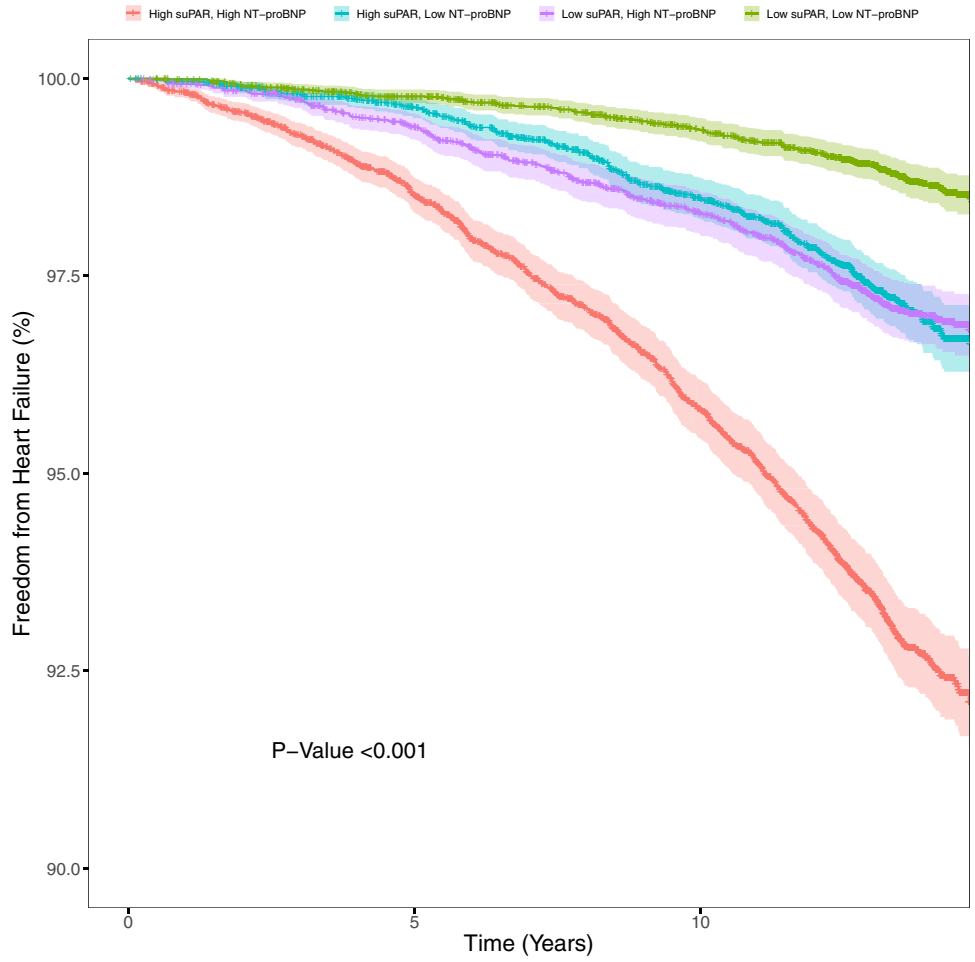
Depiction of Incident Heart Failure Risk Across Continuous Proteomics-Based suPAR Levels in the Entire Study Sample (A), Men (B), and Women (C). The median suPAR value was selected as the reference value. Sex-specific medians were designated as reference values for sex-specific analyses. A linear distribution in heart failure risk was observed in men (B), while a J-shaped curve is present in women (C). This suggests a comparatively higher risk of incident heart failure at lower and higher suPAR levels in women than in men. suPAR = soluble urokinase plasminogen activator receptor.

levels had a 3-fold higher risk of incident HF than those without biomarker elevation. Furthermore, the combination of both elevated suPAR and NT-proBNP levels provided superior risk estimation for incident heart failure than an elevation in either biomarker alone, suggesting that suPAR provides improvement to incident heart failure risk prognostication distinct from isolated natriuretic peptide elevation. A significant interaction between suPAR and sex and their association with incident heart failure risk was also observed, such that suPAR was more strongly associated with incident heart failure risk in women compared to men. Lastly, we show that the addition of suPAR levels to a model that included demographics, traditional risk factors, NT-proBNP, and CRP levels significantly enhanced the model's ability to explain the variability of incident HF risk.

suPAR plays a major role in predicting the incidence and progression of kidney and atherosclerotic cardiovascular diseases, conditions both linked to HF pathogenesis.[7,8] A previous study in the Swedish general population demonstrated an independent association between elevated suPAR levels and the incidence of severe cases of heart failure.[23] Importantly, however, as outcome data from this study were obtained solely from a national hospital discharge register, cases of heart failure diagnosed in the outpatient setting were not included in the study endpoint. This limits the overall generalizability of these findings and biases the heart failure phenotype that was studied to more advanced cases of heart failure alone. Subsequent studies have demonstrated a strong association between elevated suPAR levels and adverse outcomes in patients with known heart failure, with suPAR levels significantly improving risk discrimination and reclassification indices for heart failure events, even to the addition to BNP.[9,10]

Much is left to be learned about the mechanisms underlying the association between suPAR and heart failure. Our findings of increased incident heart failure risk attributable to proteomics-based suPAR levels even after adjustment for eGFR in a previously healthy cohort without CAD suggest that this association between suPAR and incident heart failure risk is likely not exclusively mediated by atherosclerotic disease nor renal dysfunction.[24-26] Moreover, given our demonstration of suPAR's association with incident heart failure risk independent and to the addition of NT-proBNP and CRP, it is reasonable to extrapolate that chronic inflammation and adverse immune activation, separate from ventricular stretch and acute, generalized inflammation, might be associated with heart failure pathogenesis. suPAR has previously been shown to be a powerful, independent predictor of HF events in patients with chronic HF when compared to CRP, and we add to these findings by demonstrating that suPAR is also superior to CRP in its association with incident HF risk in healthy individuals.[10,27] There are several potential reasons as for why suPAR is more robustly associated with incident HF risk than CRP. Circulating suPAR levels are a relatively stable marker of systemic inflammation and are unaffected by short-term

FIGURE 3 Association Between Proteomics-Based suPAR and NT-proBNP Levels With Incident Heart Failure Risk



Kaplan–meier curves demonstrate the highest risk of incident heart failure in participants with both elevated suPAR and NT-proBNP levels (red). NT-proBNP = N-terminal pro B-type natriuretic peptide; suPAR = soluble urokinase plasminogen activator receptor.

pathophysiological insults, unlike CRP and other acute phase reactants. Furthermore, suPAR may also capture important elements of HF pathogenesis not represented by CRP, such as immunomodulatory responses and fibrotic tissue remodeling.[28] From a comparative perspective, our findings indicate that suPAR significantly outperforms CRP in explaining the variability of incident HF risk. CRP levels provide additional but substantially less explanatory value when added to models that include suPAR. As such, suPAR may represent a superior clinical biomarker for capturing the variability in incident HF risk in the general population when compared to CRP.

Our findings lay the groundwork for future studies to examine if a causative link exists between elevated suPAR levels and incident heart failure and suggest that detecting elevated suPAR levels in previously healthy patients identifies a group that is at higher risk for developing incident heart failure. In future clinical trials, this population could also represent ideal candidates who might derive benefit from uPAR monoclonal antibodies or related therapies.[29]

STRENGTHS AND LIMITATIONS. Our study has several strengths. We analyzed a population-based sample recruited across a broad geographical region of the United Kingdom with a considerably long follow-up period. The sample had excellent representation of women (55%) (**Table 1**), which contributed to uncovering an interaction between sex and suPAR levels, such that at lower and higher proteomics-based suPAR levels, women have a

comparatively higher risk of incident heart failure than men (**Figure 2**). This finding may be reflective of differences in baseline levels of chronic inflammation between men and women or could be a result of sex-specific hormonal interactions with immune pathways.[12] Our utilization of competing-risk regression over Cox regression allowed for direct handling of the competing risk of death prior to a potential onset of incident heart failure. Importantly, our study endpoint of incident heart failure incorporated cases of heart failure diagnosed in both the outpatient and inpatient settings, encompassing the entire spectrum of new-onset heart failure diagnoses. All analyses were adjusted for both NT-proBNP and CRP levels to highlight the association of suPAR with incident heart failure risk independent of ventricular stretch and generalized inflammation. Prior to our study, the association between suPAR levels and incident heart failure subtypes by ischemic or nonischemic etiology had not been explored, nor had there been a granular approach to assessing the ability of suPAR levels to explain the variability of incident heart failure risk in a large general population sample.

Our study has important limitations to be considered. The correlation between Olink-based suPAR levels and gold-standard immunoassay methods is modest ($r = 0.57$), and Olink-based suPAR levels appear to underestimate the ability of suPAR to discriminate the risk of cardiovascular-related outcomes, such as cardiovascular death (suPARnostic suPAR [immunoassay], c-statistic 0.619; Olink suPAR, c-statistic 0.582).[13] As such, our findings may similarly underestimate the strength of the association between suPAR levels and incident HF risk. Given that the UK Biobank does not include echocardiographic data, we were unable to stratify our analyses by echocardiographic metrics such as ejection fraction. And although our investigation into the association between suPAR levels and incident and nonischemic heart failure subtypes is novel, our definition of these heart failure subtypes relied on the temporal relationship of ICD code-based diagnoses, due to the lack of echocardiographic data. A similar lack of participant-level use of guideline-directed heart failure therapies precluded the ability to adjust for confounding related to these factors.

CONCLUSIONS

In healthy participants, elevated proteomics-based suPAR levels were significantly associated with the risk of new-onset heart failure, independent of demographics, traditional risk factors, NT-proBNP levels, and CRP levels. suPAR levels were also independently associated with incident ischemic and nonischemic heart failure risk and improved the explained variability of incident heart failure risk when added to multivariable-adjusted risk models that included NT-proBNP and CRP levels. Whether suPAR plays a causative role in the development of heart failure is unknown, and whether the identification of elevated suPAR levels by screening in those at risk for heart failure could mitigate future heart failure risk should be investigated further.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Heart failure is a complex clinical syndrome associated with significant morbidity and mortality and can arise due to a multitude of distinct biological phenomena. suPAR is a circulating glycoprotein released into the bloodstream during immune activation and inflammation. We show that proteomics-based suPAR levels are significantly associated with the risk of developing ischemic and nonischemic heart failure in a large general population sample, independent of the well-validated biomarker of ventricular stretch, NT-proBNP, as well as other important clinical variables. Additionally, we show that the inclusion of both suPAR and NT-proBNP to a risk model containing demographics and traditional risk factors resulted in the strongest association with incident heart failure risk, suggesting that the presence of chronic inflammation and immune activation provides incremental prognostic information beyond that of ventricular stretch alone for incident heart failure risk.

TRANSLATIONAL OUTLOOK: As suPAR has been implicated in its association with heart failure severity in those with known heart failure and now with incident ischemic and nonischemic heart failure risk in the general population, further research is needed to understand if there is a causal association between suPAR levels and heart failure. Future analyses might also explore whether fluctuation in suPAR levels affects heart failure incidence and severity.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.