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MAJOR ARTICLE

Biological and Clinical Implications of the Vascular Endothelial Growth Factor Coreceptor Neuropilin-1 in Human Immunodeficiency Virus

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Plasma vascular endothelial growth factor (VEGF) coreceptor neuropilin-1 (NRP-1) had the largest association with coronary plaque in the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) proteomics analysis. With little known about NRP-1 in people with human immunodeficiency virus (PWH), we explored its relation to other proteins in REPRIEVE and validated our findings through a Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) case-cohort study by assessing its relation to host factors and incident cardiovascular disease and cancer. Within REPRIEVE, NRP-1 was associated with proteins involved in angiogenesis, signal transduction, immunoregulation, and cell migration/adhesion. Within CNICS, NRP-1 was associated with key host factors, including older age and male sex. NRP-1 was associated with an increased hazard of multiple cancers but a decreased prostate cancer risk. Finally, NRP-1 was most strongly associated with mortality and type 2 myocardial infarction. These data suggest that NRP-1 is part of a clinically relevant immunoregulatory pathway related to multiple comorbidities in PWH.

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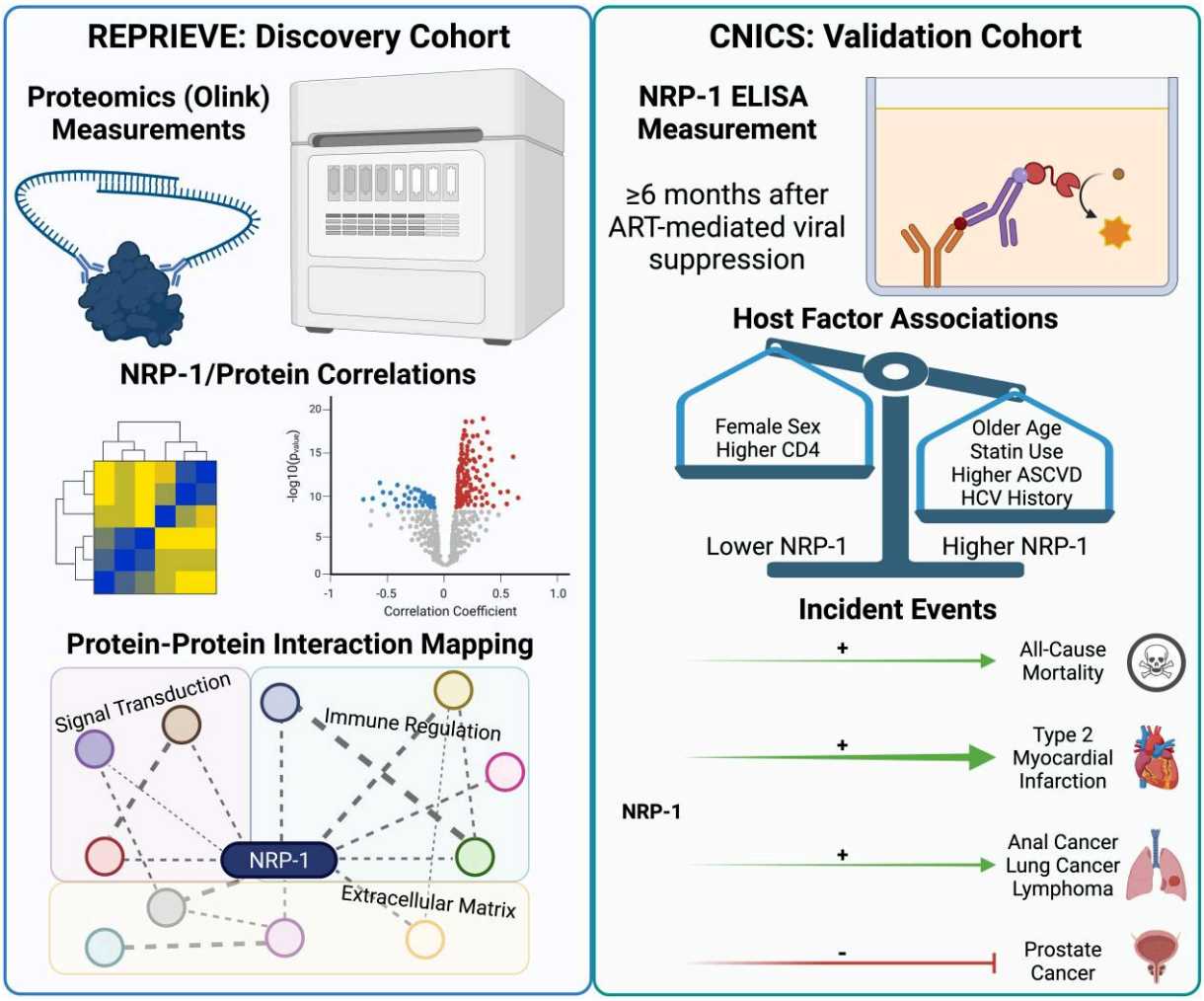
Graphical Abstract



Keywords. cancer; cardiovascular disease; HIV; neuropilin-1; VEGF.

Despite antiretroviral therapy (ART), people with human immunodeficiency virus (PWH) face an increased risk of cardiovascular disease (CVD) and malignancy, in part from persistent immune activation [1]. Recently, a proteomics approach was employed to assess relationships with coronary atherosclerosis among PWH enrolled in the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) substudy [2]. The largest effect size associated with plaque was observed with neuropilin-1 (NRP-1); each doubling was associated with 3- to 5-fold higher odds of plaque and coronary calcium. Expressed on multiple cell types, NRP-1 is a transmembrane receptor for vascular endothelial growth factor (VEGF) and class 3 semaphorins [3]. NRP-1 was initially identified relating to signal transduction, cell migration, angiogenesis, and vascular permeability [3]. In pathologic states, NRP-1 is most studied in malignancy, where increased plasma and tissue expression is associated with worse outcomes across numerous cancers [4, 5]. NRP-1 also has key immunologic functions involving T-cell maturation, upregulation on activated $CD4^+$ T cells, and an immunoregulatory and cell migration role with T-regulatory (Treg) cells and macrophages [6, 7]. Knowledge gaps remain, however, as to NRP-1's role in human immunodeficiency virus (HIV) or CVD [8–10].

Given the initial REPRIEVE findings, we explored the role of NRP-1 in CVD and malignancy among PWH. We incorporated plasma proteomics from REPRIEVE to assess the association of NRP-1 with other proteins. We also leveraged a case-cohort study within the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) as a validation cohort to evaluate NRP-1's association with other immune pathways, host factors, and adjudicated clinical events [11, 12].

METHODS

Cohorts

REPRIEVE enrolled ART-treated PWH aged 40–75 years with low-to-moderate traditional CVD risk. Participants from the substudy (a subset of United States–based participants) with available proteomics were included, representing a large subset of the substudy [2, 13, 14].

First eligible samples from CNICS participants aged ≥18 years with ≥6 months of viral suppression from 1 January 2010 were included (Figure 1). A random 1000 selected from the eligible 9430 participants resulted in 968 "subcohort" participants (32 excluded for unavailable plasma, CNICS withdrawal, and possible spontaneous viral control). Incident cases from all eligible 9430 participants with type 1 or type 2 myocardial infarction (T1MI or T2MI, respectively), ischemic stroke, venous thromboembolism (VTE), lung, anal, or prostate cancer, and non-Hodgkin lymphoma (NHL) were included. Each event's analytic cohort is formed from all participants with a specific event and the entire subcohort (because the subcohort was selected randomly, a proportion will have had an event, standard in case-cohort designs), allowing for an unbiased risk estimate [15]. All-cause mortality and incident diabetes mellitus were assessed in the subcohort alone due to sufficient events. All events were adjudicated [16]. Participants were censored at death, last laboratory or clinical visit, or site-specific end adjudication (last clinical data available through 31 December 2019).

Proteomics

Fasting plasma samples were assessed at study entry in REPRIEVE to quantify 275 unique proteins using Olink Target 96 Cardiovascular III, Immuno-oncology, and Cardiometabolic panels. Detailed methods, exclusion of proteins, and individual measurements have been described, resulting in 246 proteins for analysis [2].

Biomarkers

Among CNICS participants, the first available plasma from study entry was assessed. NRP-1 was measured by enzyme-linked immunosorbent assay (ELISA) in duplicate (Meso Scale Discovery [MSD], lower limit of detection 18 pg/mL). C-reactive protein (CRP), interleukin 6 (IL-6), interferon-inducible protein (IP-10 or CXCL10), soluble urokinase plasminogen activator receptor (suPAR), intercellular adhesion molecule 1 (ICAM-1), soluble tumor necrosis factor receptor 1 and 2 (sTNFR1 and sTNFR2, respectively) (MSD); interleukin 18 (IL-18), lipopolysaccharide-binding protein (LBP), soluble CD14 (sCD14), soluble CD163 (sCD163) (R&D Systems); and cytomegalovirus (CMV) immunoglobulin G (IgG) titer (Genway) were measured in duplicate. Kynurenine-to-tryptophan (KT) ratio was assessed in singlicate via high-performance liquid chromatography–tandem mass spectrometry.

Statistical Analysis

Spearman correlation coefficients were calculated between NRP-1 and proteins. False discovery rate–corrected *P* values were calculated by the Benjamini-Hochberg method [17]. The Search Tool for the Retrieval of Interacting Genes/Proteins (STRING, https://string-db.org/) knowledge-based protein–protein interaction database was used to assess relationships between proteins with correlation coefficients ≥0.35, using functional and physical associations, all data sources, and medium-level confidence (0.4). Enrichment analysis was not performed due to lack of sufficient background.

Among CNICS subcohort participants, Spearman correlation coefficients were calculated between NRP-1 and biomarkers. Relative differences between NRP-1 and host factors were reported with 95% confidence intervals (CIs) based on studentized range statistics [18]. Statistical significance for differences between NRP-1 and parameters was assessed by analysis of variance and level-specific significance by Tukey honest significant difference method [19]. A multivariate linear regression of $\log_{10}$ NRP-1 included all univariate associations with $P < .2$.

The association between NRP-1 (normalized to the subcohort interquartile range [IQR]) and events was assessed via Cox proportional hazards modeling with robust sandwich variance estimators and inverse probability sampling weights based on cohort versus event status [20]. Adjusted models reporting hazard ratios (HRs) with 95% CIs were developed based on observed effect size of host factor associations with NRP-1, accounting for plausible confounders in cancer and noncancer events and limiting the covariate number to avoid overadjustment.

Statistical tests were 2-tailed; an α level of .05 guided statistical inference. All analyses were performed in R software (version 4.1.3).

Investigation of HIV–NRP-1 Relationship

Based on our findings below, we subsequently assessed plasma NRP-1 (by ELISA) in a cross-sectional cohort of ART-treated PWH and age- and sex-matched HIV-negative participants recruited from the SCOPE/Options cohort (University of California, San Francisco) [21]. NRP-1 was compared by HIV status.

Patient Consent Statement

REPRIEVE received approval from the Mass General Brigham Human Research Committee and institutional review boards (IRBs) at each study site. CNICS received IRB approval from each study site. Participants provided written informed consent for the parent studies.

RESULTS

Participant Characteristics

Participants drawn from the REPRIEVE substudy (n = 734) and CNICS subcohort (n = 968) shared similar features

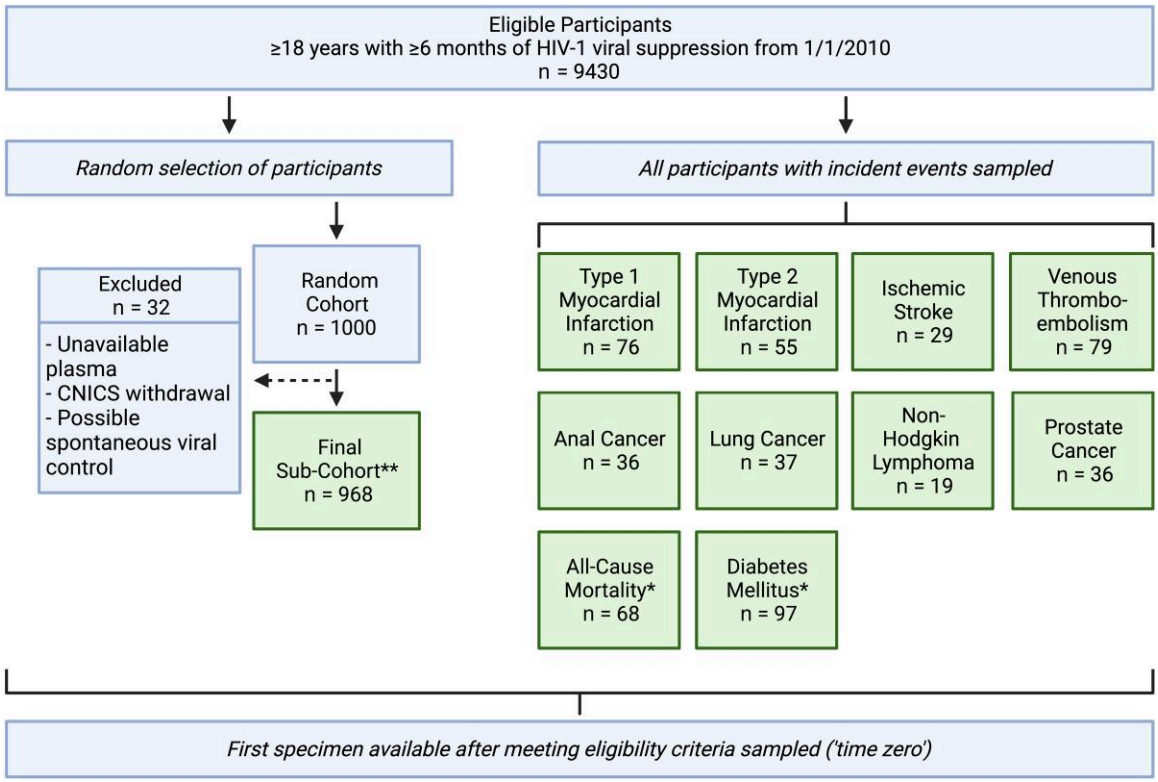


Figure 1. Diagram of the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) case-cohort study design. CNICS participants were considered eligible if they were aged ≥18 y with ≥6 mo of human immunodeficiency virus type 1 (HIV-1) viral suppression starting from 1 January 2010. From these eligible participants, a random group of 1000 participants was selected, with a final "subcohort" of 968 participants after exclusions. Also from all eligible participants, participants with any incident event were sampled (*those with incident all-cause mortality and diabetes mellitus were not oversampled, but rather only came from the subcohort due to sufficient event numbers). **Because the subcohort was selected randomly, a proportional percentage of these participants also may have had an event. The first specimen available from each participant from the subcohort or specifically identified as an event was sampled. This specimen date is considered as time zero for time-to-event analysis. An analytic cohort was created for each event, which consisted of participants who had an event and all participants in the subcohort. Time-to-event analysis (Cox proportional hazards modeling) was performed for each event using the event-specific analytic cohorts as above with sampling weights based on subcohort versus event status, which allows for an unbiased estimate of the hazard ratio. Created with BioRender.com.

(Table 1). Median age was 50 and 47 years in REPRIEVE and CNICS, respectively. In both cohorts, almost 20% were women, and participants represented a diverse range of racial and ethnic groups. Body mass index (BMI) and atherosclerotic cardiovascular disease (ASCVD) score were similar. Participants in CNICS had a higher prevalence of diabetes due to REPRIEVE enrollment criteria limiting people with diabetes. Both cohorts had comparable current and nadir $CD4^+$ T-cell distributions. Virtually all participants had HIV-1 RNA <400 cells/mL.

Results From REPRIEVE

Proteomic Correlations

Correlations of ≥0.45 and ≥0.35 with NRP-1 were identified in 5 and 25 Olink proteins, respectively (Figure 2, Supplementary 1 and Table 2). The top 5 proteins were vascular cell adhesion molecule 1 (VCAM-1, 0.54), neurogenic locus notch homolog protein 1 (0.49), growth arrest–specific protein 6 (0.47), endoglin (0.47), and oncostatin M receptor (0.46). A protein–protein interaction network was created via STRING with 10 imputed proteins (Figure 3*A*). K-means clustering resulted in 3 groups (number of groups chosen qualitatively) with 8, 15, and 13 proteins to identify functional associations (Figure 3*B*). Cluster 1's main reactome pathway was immunoregulatory interactions, with gene ontology pathways including cell/leukocyte adhesion and interferon-gamma (IFN-γ)–mediated signaling. Cluster 2's primary reactome pathway was signal transduction pertinent to migration and angiogenesis regulation and cell differentiation. Cluster 3's main reactome pathway was extracellular matrix (ECM) associated with stress/hypoxia response and cell proliferation regulation.

Results From CNICS

Biomarker Correlations

NRP-1 was related to 13 biomarkers previously assessed in CNICS that are persistently elevated despite ART and associated with non-AIDS-related events (Figure 4, Supplementary Figure 1). The strongest correlation was with sCD163 (rho [ρ] = 0.37,

Table 1. Participant Characteristics of People With Human Immunodeficiency Virus From the REPRIEVE and CNICS Studies

Characteristic	REPRIEVE	CNICS
No. of participants	734	968
Age, y, median (Q1–Q3)	50 (46–55)	47 (39–53)
Natal sex		
Male	603 (82)	799 (83)
Female	131 (18)	169 (17)
Race/ethnicity[a]		
White	383 (52)	379 (39)
Black	271 (37)	447 (46)
Hispanic	174 (24)	108 (11)
Current/former cigarette smoking	414 (56)	441 (46)
Current/former substance use[b]	378 (51)	166 (17)
BMI, kg/m^2, median (Q1–Q3)	27.0 (24.3–30.3)	26.1 (23.5–30.0)
Diabetes mellitus	2 (0.3)	125 (13)
HTN or use of anti-HTN medication	238 (32)	345 (36)
ASCVD risk score, %, median (Q1–Q3)	4.5 (2.6–6.9)	4.5 (1.7–8.9)
0 to <2.5	168 (23)	319 (33)
2.5 to <5	243 (33)	244 (25)
5 to <7.5	177 (24)	111 (11)
7.5–10	99 (13)	79 (8.2)
>10	47 (6)	215 (22)
HBV history	19 (3)	50 (5)
HCV history	24 (3)[c]	163 (17)
INSTI use	318 (43)[d]	291 (30)
PI use	131 (18)[d]	379 (39)
NNRTI use	187 (25)[d]	400 (41)
CD4 count, current, cells/μL, median (Q1–Q3)	602 (425–780)	573 (401–800)
CD4 count, nadir, cells/μL		
<50	160 (22)	189 (20)
50–199	211 (30)	219 (23)
200–349	199 (28)	240 (25)
≥350	143 (20)	320 (33)
HIV-1 RNA <400 cells/mL	708 (97)	968 (100)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CNICS, Centers for AIDS Research Network of Integrated Clinical Systems; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus type 1; HTN, hypertension; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q1, quartile 1; Q3, quartile 3; REPRIEVE, Randomized Trial to Prevent Vascular Events in HIV.

[a]CNICS uses a combined race/ethnicity description, whereas REPRIEVE separately describes race and ethnicity (totals within REPRIEVE are >100%).

[b]Refers only to injection drug use in CNICS.

[c]REPRIEVE reports active HCV infection, whereas CNICS compiles any history of HCV infection.

[d]An additional 3.5% and 9.8% were on a nucleoside reverse transcriptase inhibitor (NRTI)–sparing regimen or another NRTI-containing regimen, respectively.

$P < .001$). Others with statistically significant correlations included sTNFR2 (ρ = 0.32), KT ratio (ρ = 0.27), sTNFR1 (ρ = 0.27), suPAR (ρ = 0.26), IL-18 (ρ = 0.24), and ICAM-1 (ρ = 0.20), though these were generally modest ($P < .001$ for all). Other markers of generalized inflammation (CRP, IL-6), microbial translocation (LBP, sCD14), and CMV IgG titer had weaker or statistically nonsignificant correlations.

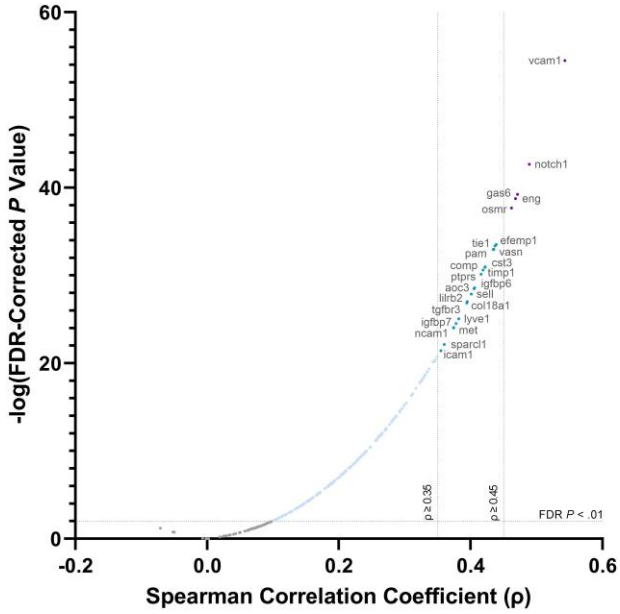


Figure 2. Proteomic correlations among people with human immunodeficiency virus within the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE). Spearman correlations of 245 proteins (Olink Target 96 Cardiovascular III, Immuno-oncology, and Cardiometabolic) with neuropilin-1 within REPRIEVE. Vertical lines delineate Spearman correlation coefficients ≥0.35 and ≥0.45. Horizontal line delineates false discovery rate (FDR)–corrected $P < .01$. Proteins with coefficients ≥0.35 are labeled.

Host Factors Associations

We assessed how clinical parameters related to plasma NRP-1 in CNICS (Table 2). Age was strongly associated: participants aged ≥60 years had a 16.1% higher NRP-1 compared to those aged <40 years ($P < .001$). Men demonstrated a 13.2% higher NRP-1 versus women ($P < .001$). There was evidence of differences by race and ethnicity but not BMI. Higher ASCVD risk was associated with higher NRP-1 (group $P < .001$). Those with a history of injection drug use (IDU) and active or prior hepatitis C virus (HCV) infection had a 6.4% ($P = .03$) and 19.3% ($P < .001$) higher NRP-1, respectively, versus those without such history. Lower current CD4 was associated with higher NRP-1: current CD4 count <401 cells/μL (quartile 1) associated with a 9%–12% higher NRP-1 compared with higher current CD4$^+$ T-cell count quartiles (group $P < .001$). In multivariate modeling, higher NRP-1 remained associated with older age, male sex, white race, current/former cigarette smoking, HCV history, and lower current CD4 count (Supplementary Table 3).

Events Modeling

We assessed the association of NRP-1 with incident events within CNICS, including all-cause mortality (n = 68), T1MI (n = 76), T2MI (n = 55), ischemic stroke (n = 29), VTE (n = 79), incident diabetes (n = 97), anal cancer (n = 36),

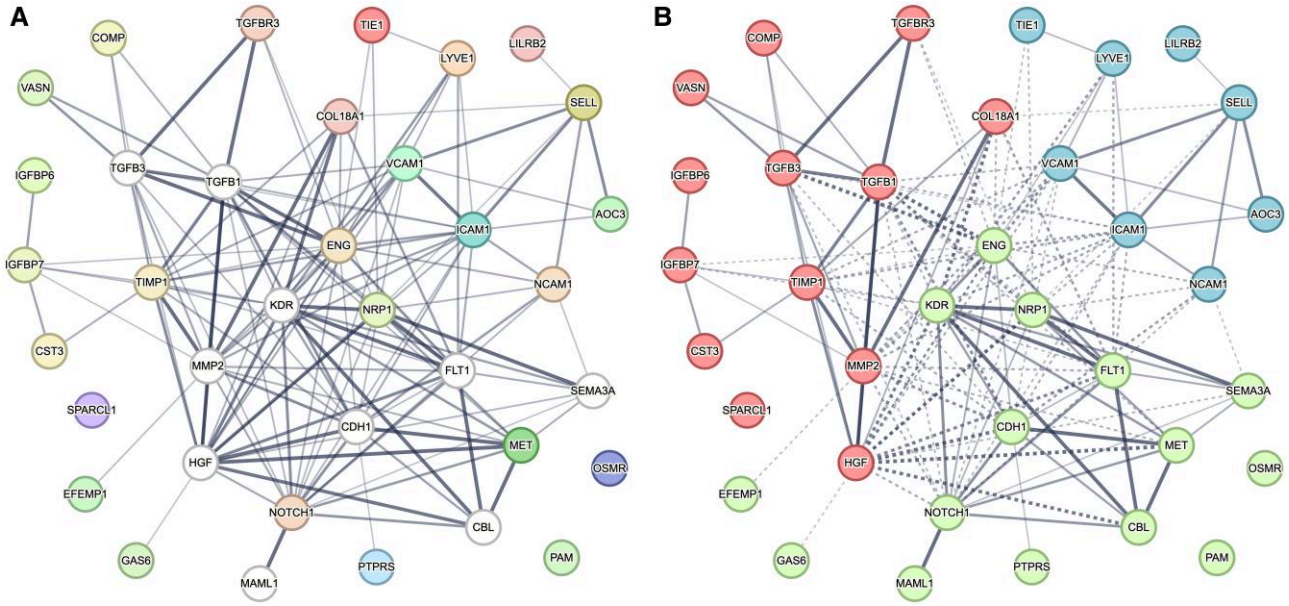


Figure 3. Protein–protein interaction maps of people with human immunodeficiency virus within the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE). *A*, Protein interaction map of neuropilin-1 (NRP-1) and all proteins with Spearman correlation coefficients ≥0.35 with NRP-1 within REPRIEVE via STRING. Relationships were generated using functional and physical associations, all data sources, and a medium-level confidence (0.400) as the minimum required interaction score. Imputed proteins are shown in white circles. Line thickness indicates the strength of supporting data for an association. *B*, K-means clustering was qualitatively employed to identify 3 clusters of 13 (red, extracellular matrix reactome), 15 (green, signal transduction reactome), and 8 (blue, immunoregulatory reactome) related proteins among all proteins with Spearman correlation coefficients ≥0.35 with NRP-1 and NRP-1 within REPRIEVE. Solid and dotted line thickness indicates strength of supporting data for an association between proteins within the same cluster and between proteins from separate clusters, respectively.

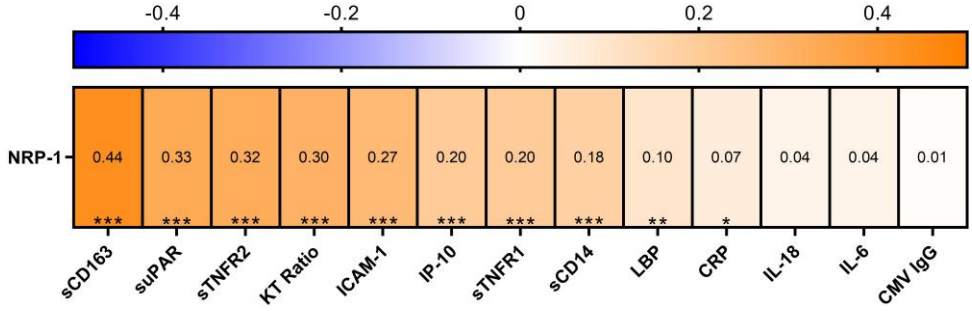


Figure 4. Biomarker correlations with neuropilin-1 (NRP-1) among people with human immunodeficiency virus within the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS). Heat map of correlations between NRP-1 and biomarkers of immune activation and inflammation within CNICS, with Spearman correlation coefficients and unadjusted *P* values. Statistical significance: **P* < .05, ***P* < .01, ****P* < .001. See Supplementary Figure 1 for associated scatter plots. Abbreviations: CMV, cytomegalovirus; CRP, C-reactive protein; ICAM-1, intercellular adhesion molecule 1; IgG, immunoglobulin G; IL-6, interleukin 6; IL-18, interleukin 18; IP-10, interferon-inducible protein; KT ratio, kynurenine-to-tryptophan ratio; LBP, lipopolysaccharide-binding protein; NRP-1, neuropilin-1; sCD14, soluble CD14; sCD163, soluble CD163; sTNFR, soluble tumor necrosis factor receptor; suPAR, soluble urokinase plasminogen activator receptor.

lung cancer (n = 37), NHL (n = 19), and prostate cancer (n = 36) (Figure 5, Supplementary Table 4). Median follow-up time from sampling was 3–5 years depending on event due to site adjudication date differences. Cancer models were adjusted for age, natal sex, HCV history, current/former cigarette smoking, and current CD4 count, while noncancer models were adjusted for ASCVD risk, HCV history, current CD4, and statin use. Each IQR increase in NRP-1 was independently associated with a 1.58 times increased hazard (95% CI, 1.13–2.23; $P = .008$) of all-cause mortality and a striking 2.83 times increased hazard (95% CI, 1.54–5.19; $P < .001$) of T2MI. Further adjustment for IDU history did not alter effect sizes. While NRP-1 was not associated with T1MI, ischemic stroke, VTE, or diabetes mellitus, it was associated with incident cancer events: every IQR increase in NRP-1 was associated with a HR of

Table 2. Host Factor Associations With Neuropilin-1 Among People With Human Immunodeficiency Virus Within the Centers for AIDS Research Network of Integrated Clinical Systems

Characteristic	Median NRP-1, ng/mL (Q1–Q3)	Percentage Difference (95% CI)	*P* Value	Group *P* Value
Age, y				
<40	322 (272–386)	Ref.		<.001
40–49	339 (276–410)	2.1 (–4.9 to 9.2)	.44	
50–59	371 (301–464)	15.8 (8.4–23.1)	<.001	
≥60	374 (298–471)	16.1 (10.5–26.2)	<.001	
Sex				
Male	353 (294–426)	Ref.		
Female	302 (243–368)	–13.2 (–18.1 to –8.4)	<.001	
Race/ethnicity				
White	362 (300–433)	Ref.		<.001
Black	327 (269–405)	–9.1 (–17.4 to –3.7)	<.001	
Hispanic	328 (275–424)	–4.9 (–12.8 to 4.1)	.18	
BMI, kg/m^2				
<25	351 (292–435)	Ref.		.16
25–29.9	343 (289–420)	–1.2 (–6.6 to 4.3)	.61	
≥30	338 (267–411)	–4.8 (–10.9 to 1.2)	.06	
Statin use, current				
No	337 (276–415)	Ref.		
Yes	373 (304–450)	7.5 (2.8–12.2)	.002	
Cigarette smoking history				
No	347 (289–425)	Ref.		
Yes	338 (276–417)	–3.3 (–7.2 to .7)	.11	
ASCVD risk score, %				
0 to <2.5	330 (279–392)	Ref.		<.001
2.5 to <5	342 (283–423)	4.5 (–3.3 to 12.2)	.11	
5 to <7.5	356 (295–447)	9.5 (1.5–20.5)	.009	
7.5–10	337 (281–410)	2.4 (–9.0 to 13.8)	.56	
>10	366 (295–451)	12.4 (4.4–20.4)	<.001	
Injection drug use history				
No	340 (281–417)	Ref.		
Yes	364 (295–448)	6.4 (.6–12.1)	.03	
HBV history				
No	342 (283–420)	Ref.		
Yes	378 (290–472)	6.0 (–4.0 to 16.2)	.23	
HCV history				
No	336 (279–408)	Ref.		
Yes	415 (324–485)	19.3 (13.1–25.6)	<.001	
INSTI use				
No	336 (279–408)	Ref.		
Yes	415 (324–485)	8.8 (–4.1 to 13.5)	<.001	
PI use				
No	342 (286–417)	Ref.		
Yes	343 (282–438)	4.2 (–.01 to 8.4)	.06	
NNRTI use				
No	353 (290–435)	Ref.		
Yes	333 (280–411)	–6.1 (–10.0 to –2.2)	.002	
Current CD4 count, cells/μL				
<401 (quartile 1)	366 (301–460)	Ref.		<.001
401–573 (quartile 2)	340 (272–415)	–11.2 (–18.1 to –4.2)	<.001	
574–800 (quartile 3)	329 (282–423)	–11.5 (–18.4 to –4.7)	<.001	
>800 (quartile 4)	343 (287–411)	–8.9 (–15.7 to –2.0)	<.001	
Nadir CD4 count, cells/μL				
<50	340 (287–425)	Ref.		.25
50–199	357 (284–442)	3.4 (–4.7 to 11.5)	.28	
200–349	341 (279–426)	–1.0 (–9.0 to 6.9)	.73	
≥350	342 (287–405)	–2.1 (–9.6 to 5.3)	.46	

Median NRP-1 level with first and third quartile ranges by host factor exposure within Centers for AIDS Research Network of Integrated Clinical Systems, with associated percentage differences and 95% CIs. Each parameter was assessed by analysis of variance with overall group and level-specific *P* values reported.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRP-1, neuropilin-1; PI, protease inhibitor; Q1, quartile 1; Q3, quartile 3.

2.08 (95% CI, 1.25–3.46; $P = .005$) for anal cancer and 2.94 (95% CI, .77–11.3; $P = .12$) for NHL. NRP-1 was associated with lung cancer in unadjusted analysis only ($P = .008$). Interestingly, NRP-1 was associated with a decreased risk of prostate cancer (HR, 0.31 [95% CI, .11–.89]; $P = .03$). Given the limited cancer cases and effect directionality, a composite of lung and anal cancer and NHL was created, for which NRP-1 was associated with a HR of 1.80 (95% CI, 1.08–3.00; $P = .02$). Supplementary analyses were performed with adjustment for age and sex; age, sex, and race instead of ASCVD risk; current CD4 by quartile; and models adjusted for all parameters that were statistically significantly associated with NRP-1 in univariate analysis. These adjustments did not affect the inferences above.

Preliminary Investigation of HIV–NRP-1 Relationship

Given NRP-1's association with mortality and T2MI among PWH but a dearth of evidence in the general population, we explored NRP-1's relationship with HIV status. Leveraging a cross-sectional cohort of ART-treated PWH (n = 164) and age- and sex-matched HIV-negative participants (n = 41), we observed no evidence of a difference in mean plasma NRP-1 by HIV status ($P = .92$) [21].

DISCUSSION

While persistent immune activation contributes to the increased risk of comorbidities among PWH, the underlying intersecting pathways are not fully appreciated. Plasma NRP-1 was previously identified as the strongest predictor of coronary plaque indices among PWH [2]. While NRP-1's function has been related to signal transduction and angiogenesis with significance in malignancy, its function in and relation to HIV is unknown. Leveraging proteomics from REPRIEVE and clinical data from CNICS to validate the initial findings, we addressed this gap with several observations. First, NRP-1 was associated with a protein network involved in angiogenesis,

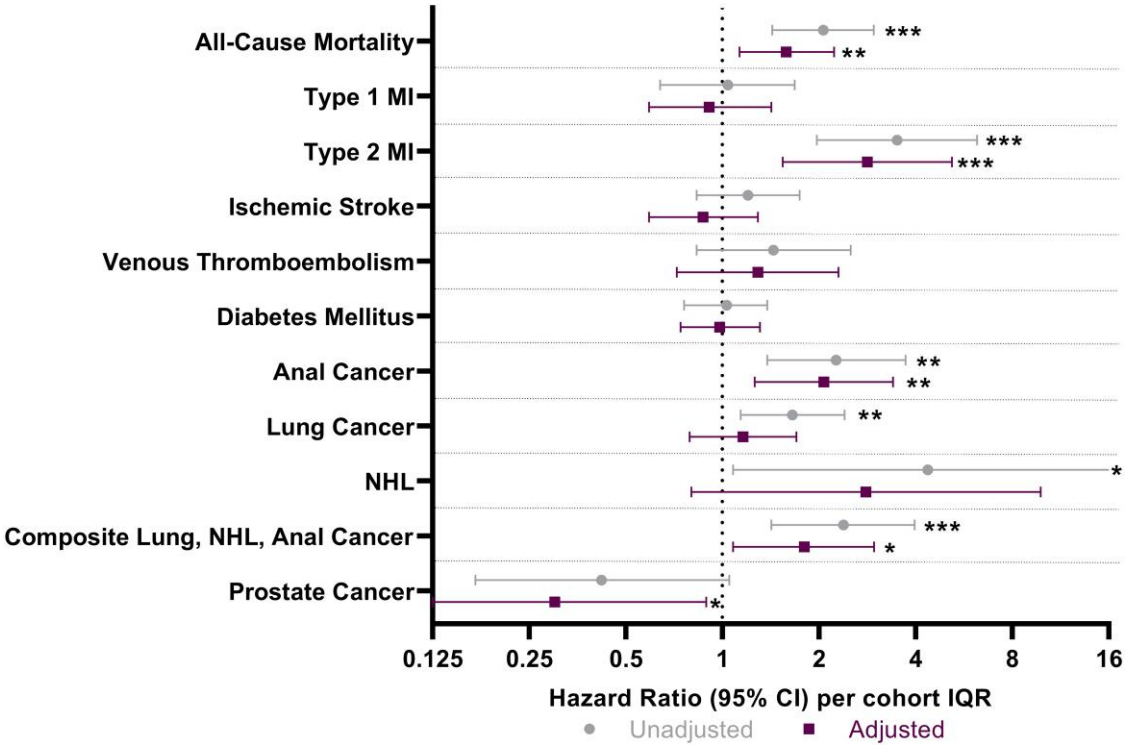


Figure 5. Association of neuropilin-1 (NRP-1) and incident events among people with human immunodeficiency virus within the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS). Forest plot of unadjusted and adjusted Cox proportional hazards models relating NRP-1 with incident events in CNICS, with associated 95% confidence intervals. Models for noncancer events were adjusted for atherosclerotic cardiovascular disease risk, statin use, hepatitis C virus (HCV) history, and current CD4 count. Models for cancer events were adjusted for age, sex, HCV history, current/former cigarette smoking, and current CD4 count. Statistical significance: $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$. Abbreviations: CI, confidence interval; IQR, interquartile range; MI, myocardial infarction; NHL, non-Hodgkin lymphoma.

signal transduction, immune regulation, and cell migration and adhesion, confirming existing data but within the context of HIV. Interestingly, NRP-1 only modestly related to major inflammatory pathways that are elevated in PWH. Second, NRP-1 was associated with key host factors, with higher levels in those who were older, men, and had a history of HCV or lower current CD4. Finally, NRP-1 was associated with multiple forms of incident cancer and all-cause mortality. Most strikingly, NRP-1 was associated with T2MI with the largest effect size compared to other biomarkers previously assessed [12]. Our findings suggest NRP-1 as a clinically relevant immunoregulatory biomarker of multiple comorbidities in PWH.

Consistent with prior work in the general population, we observed that NRP-1 correlated with a protein network with functions including signal transduction, cell migration and adhesion, and ECM and immune regulation. These data complement NRP-1's known function in the general population but assessed here in HIV. NRP-1 has a critical role in angiogenesis through interactions with VEGF, semaphorin 3A, and ECM integrin ligands [22]. NRP-1 increases vascular permeability via disruption of endothelial barrier function—beneficial in the immediate inflammatory response for immune cell migration, but potentially detrimental in the HIV-induced chronic inflammatory state [23]. Beyond angiogenesis, NRP-1 associations and protein–protein network also support its role in key immunologic functions. NRP-1 expression appears upregulated on activated $CD4^{+}$ T cells and associated with cell exhaustion; this may coincide with our observed trend of higher NRP-1 in those with lower current $CD4^{+}$ T-cell counts [7]. While NRP-1 expression on Treg cells favors suppressing immune responses in vitro, this is abrogated in the presence of damage/pathogen-associated molecular patterns, which tend to be increased in PWH [6]. Interestingly, NRP-1 had relatively modest associations with biomarkers that are higher in and associated with morbidity and mortality in PWH. Of the biomarkers assessed, the strongest association was found with sCD163, a marker of monocyte/macrophage activation—especially immunoregulatory M2 polarization [12, 21, 24]. While VEGF is known to promote macrophage recruitment, its dependence on NRP-1 is unknown [25]. Markers of generalized inflammation, the inflammasome, and microbial translocation tended to have negligible correlations, suggesting NRP-1's mechanistic association with disease differs from those previously studied in PWH.

We also observed potentially clinically relevant associations between host factors and NRP-1. Independent associations were seen between higher NRP-1 and older age, male sex, HCV history, and lower current CD4. In mouse models, older age was associated with increased NRP-1 expression in multiple organs; this increased expression, in turn, suppressed anti-thrombotic and anti-inflammatory pathways leading to platelet and macrophage activation and fibrosis [26]. Moreover, genetic deletion of endothelial cell–specific NRP-1 reduced fibrosis. Thus, this NRP-1-related pathway may partially explain our observed association of NRP-1 with HCV. NRP-1 overexpression was observed in human cirrhotic livers caused by both HCV and steatohepatitis, suggesting relevance of NRP-1–related fibrosis more broadly [27]. As sCD163, a marker of macrophage activation (especially profibrotic M2 macrophages), is increased in PWH, associated with liver disease, and strongly correlated with NRP-1, it is plausible that NRP-1–induced macrophage activation may be particularly relevant in PWH [21, 28]. Beyond liver fibrosis, the association between higher NRP-1 and lower CD4 begs the question if NRP-1 may be associated with lymphoid fibrosis, which is well recognized in PWH despite ART [29]. The higher NRP-1 level in men versus women is interesting, as select inflammatory biomarkers tend to be higher in women as opposed to men [12, 30]. This may be related to sex hormones and genetics, though existing data is conflicting; in vitro, estradiol leads to increased NRP-1 expression, while progesterone decreased expression [31]. However, androgens have also been reported to suppress NRP-1 in vitro, suggesting that sex hormones alone cannot explain the observed sex difference [32].

The relevance of NRP-1 in malignancy is increasingly recognized, and our results highlight that in the context of HIV. NRP-1 was associated with incident anal cancer and a composite of anal and lung cancer and NHL lymphoma. Tissue and systemic NRP-1 expression has been linked to the pathogenesis of multiple cancers [33–35]. NRP-1 likely has overlapping and distinct mechanisms relating to tumor angiogenesis, cell migration and metastasis, and invasion [36]. NRP-1 also serves a critical immunoregulatory role whereby Treg cells promote immune tolerance by preferential engagement with dendritic cells over $CD4^+$ T cells through NRP-1 interactions [6, 37, 38]. Our observation that NRP-1 was associated with a decreased prostate cancer risk is novel. NRP-1 is suppressed by testosterone and increased with androgen deprivation [32]. NRP-1 overexpression is associated with metastatic and castration-resistant prostate cancer but not early-stage tumors or those with lower Gleason scores, potentially suggesting a regulatory switch at some stage or during adaptation to low-androgen environments [32, 39]. Given the relative hypogonadism of men with HIV, higher NRP-1 may correlate with lower androgen levels and a lower risk of prostate cancer [40]. Finally, it is notable that the observed effects of NRP-1 mirror the increased rates of anal and lung cancer and NHL and decreased risk of prostate cancer in PWH [41].

In addition to its association with cancer, NRP-1 was related to all-cause mortality with an effect size comparable to IL-6 and sTNFR2 in PWH [12]. Our finding may reflect the summation of comorbidities in which NRP-1 has contributing pathologic roles. Several studies have assessed systemic and tissue-level NRP-1 and associated it with mortality, but only in participants with diagnosed cancer to assess prognosis [4, 5]. None to our knowledge have evaluated all-cause mortality in a broader population without a prevalent cancer diagnosis. While we are unable to exclude potentially non-NRP-1–mediated causes of death (accidents, trauma, etc) due to unavailable data, this lack of exclusion would only bias our estimate toward the null and therefore be unlikely to explain the observed association.

Despite our previous finding in REPRIEVE that NRP-1 was associated with 3- to 5-fold increased odds of plaque, we did not observe an association of NRP-1 with T1MI in the CNICS validation cohort [2]. Mechanistically, NRP-1, as a VEGF coreceptor that mediates cross-linking with VEGF receptor 2 (KDR, which was strongly correlated with NRP-1), may have potent proinflammatory properties, including the ability to mediate leukocyte trafficking to sites of inflammation—a critical step in atherogenesis [42]. In mouse models, NRP-1 was induced by oxidized low-density lipoprotein, and NRP-1–expressing cells had reduced capacity for cholesterol efflux [10]. Moreover, $NRP\text{-}1^+$ $CD4^+$ T cells had increased migration to the aorta, were increased in atherosclerotic plaques, and were highly activated with increased IFN-γ and tumor necrosis factor–α secretion [7, 10]. The lack of evidence of an association here might represent a type 2 error or a different relationship in vivo. Longitudinal work in REPRIEVE will allow us to further evaluate the relationship between NRP-1, plaque progression, statin therapy, and CVD.

Perhaps the most interesting finding was that NRP-1 was independently associated with T2MI. Each IQR increase in NRP-1 was independently associated with an almost 3-fold increased hazard of T2MI—an effect larger than any of the other biomarkers previously assessed, all of which are considered critical inflammatory pathways [12]. Our observed association was robust to multivariate adjustment of confounders that are potentially associated with both NRP-1 and T2MI, including ASCVD and IDU [43, 44]. The etiologies underlying T2MI are heterogeneous, but the supply-demand mismatch may be due to increased collateralization, coronary endothelial or microvascular dysfunction, or myocardial fibrosis, all of which may be exacerbated in a population known to have excess plaque [14]. Increased NRP-1 leads to increased endothelial cell proliferation and activation with decreased vascular maturity and reduced adhesion to the ECM [45, 46]. VCAM-1 and ICAM-1 (strongly associated with NRP-1) are upregulated in

proinflammatory environments, where endothelial cell detachment from the underlying ECM occurs, increasing permeability and leukocyte migration [47]. Finally, as NRP-1 has been shown to enhance tranforming growth factor–β signaling and appears to be involved in liver, kidney, and pulmonary fibrosis, NRP-1 could plausibly lead to myocardial fibrosis, which is known to be increased in PWH [9, 27, 48, 49]. Future evaluation of specific T2MI etiology associations with NRP-1 may help to better delineate these mechanisms.

Study strengths include the leveraging of 2 large contemporary cohorts comprised of relevant populations of longstanding ART-controlled PWH with centrally adjudicated outcomes. However, the study has several limitations. Though our work demonstrates the clinical relevance of NRP-1 among PWH, and NRP-1 is known to be elevated in other inflammatory states, the specific relevance of NRP-1 in PWH compared to the general population is unknown [50]. In a preliminary investigation, we did not observe a difference in plasma levels of NRP-1 between PWH and HIV-negative controls. This may be underpowered, or a clinically relevant interaction may exist whereby changes in NRP-1 are more predictive of outcomes in PWH compared to the general population irrespective of comparable NRP-1 levels. Finally, while we do not know the relation of plasma and tissue NRP-1 or differential tissue expression, these data highlight that circulating NRP-1 may have clinical relevance in multiple comorbidities known to be increased among PWH.

In conclusion, we previously identified NRP-1 as having the largest proteomic association with coronary plaque among ART-treated PWH. We extended these findings by showing NRP-1 to be related to a protein network responsible for cell migration and adhesion, angiogenesis, ECM formation, and immune regulation, while in terms of host factors, it was most associated with age, sex, and HCV history. Additionally, we confirmed the importance of NRP-1 in cancer pathogenesis but in the context of HIV with a novel protective relationship with prostate cancer. Most importantly, we show that NRP-1 was associated with all-cause mortality and had the largest effect size in relation to T2MI compared to other inflammatory biomarkers in a key validation analysis within CNICS. While the clinical implications and underlying mechanisms require further study, NRP-1 may represent a clinically relevant biomarker and component of a larger mechanistic pathway, raising important, testable hypotheses regarding the pathogenesis of NRP-1 in HIV and non-AIDS-related events.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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