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Inflammatory biomarkers and prevalent coronary atherosclerosis among Ugandan adults with and without HIV

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Abstract

Background

Chronic inflammation is implicated in coronary atherosclerosis, particularly among people with HIV, who may experience persistent immune activation despite antiretroviral therapy. However, most evidence linking inflammatory biomarkers to coronary artery disease (CAD) comes from populations outside sub-Saharan Africa. We assessed associations between inflammatory biomarkers and CAD among older adults with and without HIV in southwestern Uganda.

Methods

We analyzed adults aged ≥ 40 years in a community-based cohort in rural southwestern Uganda. CAD was assessed using coronary artery calcium scanning and contrast-enhanced coronary computed tomography angiography. Biomarkers included indicators of macrophage activation (sCD163), hypercoagulability (D-dimer), systemic inflammation (C-reactive protein), gut epithelial integrity (fatty acid binding protein 2), and hematologic inflammatory indices derived from complete blood counts. We fitted Firth penalized logistic regression models to estimate crude, HIV-stratified, and multivariable-adjusted associations. Receiver-operating-characteristic analyses assessed whether select biomarkers improved discrimination beyond the atherosclerotic cardiovascular disease (ASCVD) risk score.

Results

Among 585 participants, mean age was 57.7 years, 287 (49.1%) had HIV, and 45 (7.7%) had CAD. Most biomarkers, including C-reactive protein, D-dimer, fatty acid–binding protein 2, and complete blood count–derived inflammatory indices, were not associated with CAD after multivariable adjustment and false-discovery-rate correction. Higher sCD163 was inversely associated with CAD in the adjusted overall model (odds ratio per 1-standard-deviation increase, 0.63; 95% confidence interval, 0.47–0.87; q = 0.048), but this finding was not consistent across HIV strata. Adding sCD163 to the ASCVD risk score did not improve discrimination for CAD.

Conclusions

In this cohort of older adults in rural Uganda, inflammatory biomarkers showed limited associations with CAD and did not improve discrimination beyond conventional risk assessment. These findings support emphasis on established cardiovascular risk assessment among older Ugandans, and further investigation into the pathogenesis of CVD risk in this population.

Background

Cardiovascular disease (CVD) remains the leading cause of death worldwide, with an increasing burden occurring in low- and middle-income countries (1). Although primary data on coronary artery disease (CAD) risk in SSA remain limited, modeling studies suggest that, if traditional and HIV-related CVD risk

are similar in Africans as among populations in the Global North, CAD may represent an important and under-recognized cause of premature death and disability in SSA (2–4).

Inflammation is well-recognized as a central mechanistic contributor of CAD plaque initiation, progression, and destabilization in the Global North (5). The inflammatory contributions to CAD may be particularly relevant to people living with HIV (PWH); despite effective antiretroviral therapy, PWH may experience persistent immune activation and low-grade systemic inflammation, which have been proposed as contributors to excess atherosclerotic cardiovascular risk (6–8). Biomarkers such as C-reactive protein, D-dimer, and soluble CD163, as well as derived indices from routine laboratory tests, have therefore attracted interest as potentially accessible markers of vascular risk (9–11). Notably, evidence supporting the inflammatory drivers of atherosclerosis extends to clinical trials of anti-inflammatory therapies, which have reduced cardiovascular events in the general population and among PWH with relatively low predicted CVD risk (12, 13). These effects appear to be independent of lipid-lowering therapy(12, 14).

However, much of the available evidence about relationships between biomarkers and coronary artery disease comes from high-income settings rather than African populations (6–8, 15, 16). Yet, there is increasing evidence that such relationships may not extrapolate to all regions and population sub-groups. For example, in the REPRIEVE study of statin use to reduce CVD events among PWH, although the effect size for CVD event reduction was similar in African populations as elsewhere, the absolute rate of events was much lower in the African sub-group (13). Moreover, studies from the United States suggest that inflammatory biomarker levels and their links to cardiovascular disease can differ across ethnic groups(17, 18), while recent Ugandan studies suggest that patterns of inflammation and CAD may also vary locally (19, 20). There remains uncertainty about whether inflammation meaningfully impacts CAD risk in African populations, and whether such associations differ by HIV status. To address this evidence gap, we examined the association between circulating inflammatory biomarkers and prevalent CAD among older adults with and without HIV in rural southwestern Uganda.

Methods

Study design and setting

This analysis was conducted on data collected as part of the epidemiology of CAD among People with HIV in Uganda Study (19). Briefly, the study enrolled community-dwelling adults aged 40 years and older from southwestern Uganda to examine CAD using coronary computed tomography imaging. Participants living with HIV (PWH) were recruited from publicly operated HIV treatment clinics in southwestern Uganda and were required to have received antiretroviral therapy for at least 3 years. HIV-negative participants were recruited from surrounding communities and were frequency-matched to participants with HIV on age and sex.

Study measures

Participants underwent cardiovascular risk profiling, including assessment of demographic characteristics, HIV status, smoking history, alcohol use, anthropometric measurements, blood pressure, glycemic status, and lipid profile. Anthropometric assessments included measurement of body weight and height, from which body mass index was calculated. Blood pressure was measured from a seated position two times with five minutes rest in between. Laboratory measurements included HbA1c, high-density lipoprotein cholesterol, total cholesterol, and triglycerides. These variables were also used to estimate predicted 10-year atherosclerotic cardiovascular disease risk. CAD was assessed using the parent study's cardiac computed tomography (CT) protocol, which included non-contrast electrocardiogram (ECG)-gated CT for coronary artery calcium scoring and contrast-enhanced coronary CT angiography (CCTA) for plaque and stenosis assessment (19). Coronary artery calcium was quantified using the Agatston method. Contrast-enhanced scans were interpreted by experienced cardiovascular imaging readers blinded to participants' HIV status and clinical characteristics, and stenosis severity was graded using the Coronary Artery Disease–Reporting and Data System (CAD-RADS)(21).

Outcome definition

CAD was defined as a composite outcome that included 1) an Agatston calcium score greater than zero on the calcium scan or 2) any evidence of plaque on the contrast-enhanced CT angiography imaging. Imaging studies were interpreted by trained cardiovascular radiologists who were blinded to participants' HIV status and clinical characteristics.

Exposures of interest

Our primary exposures of interest were circulating and derived biomarkers of inflammation selected to capture pathways plausibly linked to atherosclerotic cardiovascular disease among people with HIV, including systemic inflammation, coagulation, monocyte–macrophage activation, intestinal epithelial injury, and hematologic inflammatory balance(7, 8). Blood samples were collected at the study visit, processed to isolate plasma, and stored at − 80°C until testing.

Circulating biomarkers included high-sensitivity C-reactive protein (hs-CRP), D-dimer, fatty acid–binding protein 2 (FABP2), and Soluble CD163(sCD163). hs-CRP was included as a marker of systemic inflammation; D-dimer as a marker of coagulation activation and thrombotic risk; FABP2 as a marker of intestinal epithelial injury and gut barrier dysfunction; and sCD163 as a marker of monocyte–macrophage activation. These pathways have been implicated in HIV-associated immune activation and cardiovascular disease risk(7, 8, 22–24). hs-CRP, D-dimer, and sCD163 were measured using Multiplex Luminex assays (R&D Systems, Minneapolis, MN, USA), and FABP2 was measured using enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN, USA). Samples were assayed in

duplicate, and the mean of the two measurements was used in analysis. Assay-specific lower and upper limits of detection were applied according to laboratory quality-control procedures.

Whole blood was also analyzed for complete blood counts (CBCs), which were used to derive hematologic inflammatory indices. These indices were included as low-cost markers of systemic immune and inflammatory balance that integrate neutrophil, lymphocyte, platelet, and monocyte counts. The derived indices included the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), pan-immune-inflammation value (PIV), and monocyte-to–high-density lipoprotein cholesterol ratio (MHR). NLR and PLR reflect the balance between innate immune activation and lymphocyte-mediated immune regulation; SII, SIRI, and PIV combine multiple leukocyte and platelet components to summarize systemic inflammatory activity; and MHR combines monocyte-mediated inflammation with high-density lipoprotein cholesterol, reflecting the balance between pro-inflammatory monocyte activity and anti-inflammatory lipid pathways(9, 10).

NLR was calculated as neutrophil count divided by lymphocyte count; PLR as platelet count divided by lymphocyte count; LMR as lymphocyte count divided by monocyte count; SII as platelet count multiplied by neutrophil count and divided by lymphocyte count; SIRI as neutrophil count multiplied by monocyte count and divided by lymphocyte count; PIV as neutrophil count multiplied by platelet count and monocyte count and divided by lymphocyte count; and MHR as monocyte count divided by high-density lipoprotein cholesterol.

Covariates

Adjusted association models included HIV status, age, sex, smoking status, systolic blood pressure, HbA1c, HDL cholesterol, and LDL cholesterol. The 10-year atherosclerotic cardiovascular disease (ASCVD) risk score was considered separately in discrimination analyses (25).

Statistical analyses

To describe the relationship between inflammatory biomarkers and CAD, we first graphically assessed biomarker distributions by CAD status using boxplots and violin plots of natural-log transformed biomarker values. Next, we fitted Firth-penalized logistic regression models to reduce small-sample bias. For each biomarker, we fitted two sets of models: 1) a crude model with CAD as the outcome and the biomarker as the predictor; 2) adjusted models including the biomarker, HIV status, age, sex, smoking status, systolic blood pressure, HbA1c, HDL cholesterol, and LDL cholesterol. To explore whether associations differed by HIV status, models were repeated separately among people with HIV and people without HIV. In these models, we did not include additional covariates to avoid overfitting in strata with few CAD events. In sensitivity analyses, biomarkers were categorized into tertiles. Participants in the highest tertile were compared with those in the lower two tertiles. These tertile analyses used the

same model structure as the primary continuous-biomarker analyses: crude overall models, adjusted overall models, crude models among people with HIV, and crude models among people without HIV.

Finally, receiver-operating-characteristic analyses were performed to assess whether biomarkers that emerged in the primary or sensitivity analyses improved discrimination for CAD beyond the ASCVD risk score. These analyses compared the ASCVD risk score alone with models including biomarkers that emerged as signals in the primary association analyses. ROC analyses were performed in the overall cohort and separately among people with HIV and people without HIV. Discrimination was summarized using the area under the receiver-operating-characteristic curve, and differences in AUC were evaluated using DeLong tests.

Because multiple biomarkers were evaluated, false-discovery-rate adjustment was applied using the Benjamini–Hochberg method(26). Adjusted q values were calculated separately within each model family: crude overall, adjusted overall, crude among people with HIV, and crude among people without HIV. Both nominal p values and false-discovery-rate adjusted q values were reported.

As an exploratory secondary analysis, we repeated the continuous-biomarker models separately among men and women and fitted adjusted models including biomarker-by-sex interaction terms. All analyses were performed in R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical considerations

The study received approval from institutional review boards at the Mbarara University of Science and Technology and Mass General Brigham. All participants provided written informed consent prior to enrollment.

Results

The study recruited 625 individuals. Of these, 586 participants had coronary computed tomography imaging data available for classification of coronary artery disease (CAD). One participant with imaging data had no inflammatory biomarker measurement available, leaving 585 participants in the final analytic cohort **(**Fig. 1**).** Among these, CRP and sCD163 were available for all 585 participants, D-dimer for 583 participants, FABP2 for 448 participants, and CBC-derived inflammatory indices — NLR, PLR, LMR, SII, SIRI, PIV, and MHR — for 385 participants.

Legend: Biomarker availability varied by assay type: CRP and sCD163, 585 participants; D-dimer, 583 participants; FABP2, 448 participants; complete blood count–derived indices, 385 participants. CAD, coronary artery disease; CBC, complete blood count; CRP, C-reactive protein; FABP2, fatty acid–binding protein 2; sCD163, soluble CD163.

Among the 585 participants included in the analysis, the mean age was 57.7 years, and 300 participants (51.3%) were male. Forty-five participants (7.7%) had imaging-defined CAD. Participants with CAD were

older than those without CAD (mean age, 60.5 vs. 57.4 years; P = 0.003), were more likely to be male (73.3% vs. 49.4%; P = 0.003), and were more likely to report current smoking (17.8% vs. 7.4%; P = 0.028). Mean ASCVD risk was higher among participants with CAD than among those without CAD (9.1% vs. 5.9%; P = 0.002). BMI was lower among participants with CAD (22.6 vs. 24.2 kg/m²; P = 0.031). HIV status, alcohol status, blood pressure, lipid measures, triglycerides, and HbA1c did not differ significantly by CAD status **(**Table 1**).** For most biomarkers, the distributions were broadly similar between the two groups, with substantial overlap in median values, interquartile ranges, and individual participant values **(**Fig. 2**).**

Table 1
Baseline characteristics by coronary artery disease status.

Variable	Overall (N = 585)	CAD (n = 45)	No CAD (n = 540)	P value
HIV status				0.288
PWOH	298 (50.9%)	19 (42.2%)	279 (51.7%)	
PWH	287 (49.1%)	26 (57.8%)	261 (48.3%)	
Sex				0.003
Male	300 (51.3%)	33 (73.3%)	267 (49.4%)	
Female	285 (48.7%)	12 (26.7%)	273 (50.6%)	
Smoking status				0.028
Never smoker	344 (58.8%)	20 (44.4%)	324 (60.0%)	
Past smoker	193 (33.0%)	17 (37.8%)	176 (32.6%)	
Current smoker	48 (8.2%)	8 (17.8%)	40 (7.4%)	
Alcohol status				0.177
Never drinker	177 (30.3%)	9 (20.0%)	168 (31.1%)	
Past drinker	230 (39.3%)	23 (51.1%)	207 (38.3%)	
Current drinker	178 (30.4%)	13 (28.9%)	165 (30.6%)	
Age, years	57.7 (6.7)	60.5 (6.3)	57.4 (6.6)	0.003
ASCVD risk, %	6.1 (7.3)	9.1 (6.2)	5.9 (7.3)	0.002
SBP, mmHg	124.7 (19.5)	126.8 (21.4)	124.5 (19.3)	0.496
DBP, mmHg	79.0 (11.9)	78.3 (11.0)	79.0 (12.0)	0.670
HDL, mmol/L	1.3 (0.5)	1.2 (0.4)	1.3 (0.5)	0.381
LDL, mmol/L	2.2 (0.9)	2.3 (1.0)	2.2 (0.9)	0.292
BMI, kg/m²	24.1 (5.0)	22.6 (4.8)	24.2 (5.0)	0.031
Triglycerides, mmol/L	1.7 (1.1)	1.6 (1.0)	1.7 (1.1)	0.364
HbA1c, %	5.8 (1.2)	6.1 (1.5)	5.7 (1.1)	0.189

Footnote: *Values are presented as mean (SD) or n (%). P values compare participants with CAD and those without CAD. ASCVD denotes atherosclerotic cardiovascular disease; BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; PWH, people with HIV; PWOH, people without HIV; SBP, systolic blood pressure.*

Legend: Boxplots show natural-log transformed biomarker values by coronary artery disease status; points indicate individual observations. CAD, coronary artery disease; CRP, C-reactive protein; FABP2, fatty acid–binding protein 2; LMR, lymphocyte-to-monocyte ratio; MHR, monocyte-to–high-density lipoprotein ratio; NLR, neutrophil-to-lymphocyte ratio; PIV, pan-immune-inflammation value; PLR, platelet-to-lymphocyte ratio; sCD163, soluble CD163; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.

Associations between inflammatory biomarkers and CAD

In crude models, most inflammatory biomarkers were not associated with CAD. In models adjusted for HIV status, age, sex, smoking status, systolic blood pressure, HbA1c, HDL cholesterol, and LDL cholesterol, increasing sCD163 was inversely associated with CAD (OR, 0.63; 95% CI, 0.47–0.87; P = 0.004; q = 0.048). No other biomarker was significantly associated with CAD after false-discovery-rate correction in adjusted overall models (Table 2; Fig. 3). In models stratified by HIV status, sCD163 was inversely associated with CAD among people without HIV (OR, 0.60; 95% CI, 0.37–0.92; p = 0.020), but this association did not remain significant after false-discovery-rate correction (q = 0.225). Among people with HIV, FABP2 showed a borderline positive association with CAD (OR, 1.71; 95% CI, 0.96–3.38; p = 0.070), and MHR showed a borderline inverse association (OR, 0.65; 95% CI, 0.40–1.04; p = 0.072), but neither association persisted after accounting for false-discovery-rate correction. The remaining biomarkers were not associated with CAD in crude stratified models (Table 2).

Table 2
Biomarker associations with coronary artery disease overall and by HIV status.

Biomarker	Crude overall OR (95% CI); p/q	Adjusted overall OR (95% CI); p/q	Crude PWH OR (95% CI); p/q	Crude PWOH OR (95% CI); p/q
CRP	0.91 (0.69–1.23); 0.511/0.820	0.93 (0.70–1.26); 0.600/0.660	0.88 (0.63–1.30); 0.486/0.655	0.93 (0.62–1.53); 0.750/0.917
D-dimer	0.94 (0.73–1.29); 0.675/0.820	0.92 (0.71–1.27); 0.596/0.660	0.86 (0.63–1.27); 0.410/0.655	0.98 (0.66–1.73); 0.936/0.973
NLR	1.05 (0.71–1.54); 0.820/0.820	0.90 (0.59–1.35); 0.596/0.660	1.71 (0.91–3.33); 0.098/0.361	0.78 (0.46–1.31); 0.349/0.832
PLR	0.89 (0.62–1.32); 0.547/0.820	0.92 (0.63–1.41); 0.704/0.704	0.90 (0.56–1.70); 0.712/0.712	0.87 (0.53–1.50); 0.618/0.917
LMR	1.11 (0.75–1.61); 0.605/0.820	1.29 (0.87–1.92); 0.198/0.436	1.17 (0.70–1.82); 0.536/0.655	0.99 (0.55–1.81); 0.973/0.973
SII	0.94 (0.63–1.38); 0.744/0.820	0.85 (0.55–1.28); 0.426/0.660	1.48 (0.79–2.87); 0.222/0.489	0.70 (0.40–1.19); 0.198/0.832
SIRI	0.95 (0.64–1.40); 0.789/0.820	0.74 (0.48–1.13); 0.170/0.436	1.24 (0.69–2.22); 0.477/0.655	0.78 (0.43–1.34); 0.378/0.832
PIV	0.88 (0.59–1.29); 0.510/0.820	0.72 (0.46–1.11); 0.135/0.436	1.16 (0.64–2.16); 0.630/0.693	0.72 (0.40–1.24); 0.247/0.832
MHR	0.79 (0.54–1.17); 0.243/0.820	0.70 (0.45–1.10); 0.117/0.436	0.65 (0.40–1.04); 0.072/0.361	1.11 (0.62–1.92); 0.712/0.917
FABP2	1.27 (0.88–1.86); 0.200/0.820	1.28 (0.84–2.00); 0.252/0.463	1.71 (0.96–3.38); 0.070/0.361	0.86 (0.48–1.56); 0.604/0.917
sCD163	**0.70 (0.53–0.94); 0.018/0.203**	**0.63 (0.47–0.87); 0.004/0.048**	0.74 (0.51–1.10); 0.132/0.362	**0.60 (0.37–0.92); 0.020/0.225**

Note: Odds ratios are expressed per 1-SD increase in the natural-log transformed biomarker. Adjusted overall models included HIV status, age, sex, smoking status, systolic blood pressure, HbA1c, HDL cholesterol, and LDL cholesterol. The ASCVD risk score was not included in the adjusted association models because its component variables were included directly. HIV-stratified models were crude because of the small number of CAD events within strata. q values are Benjamini-Hochberg false-discovery-rate adjusted p values within each model family. ASCVD denotes atherosclerotic cardiovascular disease; CAD, coronary artery disease; CI, confidence interval; CRP, C-reactive protein; FABP2, fatty acid-binding protein 2; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LMR, lymphocyte-to-monocyte ratio; MHR, monocyte-to-high-density-lipoprotein ratio; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PIV, pan-immune-inflammation value; PLR, platelet-to-lymphocyte ratio; PWH, people with HIV; PWOH, people without HIV; sCD163, soluble CD163; SII, systemic immune-inflammation index; and SIRI, systemic inflammation response index.

Note

Odds ratios are expressed per 1-SD increase in the natural-log transformed biomarker. Adjusted overall models included HIV status, age, sex, smoking status, systolic blood pressure, HbA1c, HDL cholesterol, and

LDL cholesterol. Horizontal lines indicate 95% confidence intervals, and the vertical reference line indicates an odds ratio of 1.0.

In exploratory sex-stratified analyses, the inverse association between soluble CD163 and coronary artery disease was directionally similar among men and women **(Figure S1).** In adjusted models, each 1-standard-deviation increase in log-transformed soluble CD163 was associated with lower odds of coronary artery disease among men (OR, 0.60; 95% CI, 0.41–0.87; P = 0.008; q = 0.083) and showed a similar, although less precise, inverse association among women (OR, 0.68; 95% CI, 0.38–1.25; P = 0.213; q = 0.556). There was no evidence that sex modified this association (interaction OR, 1.22; 95% CI, 0.65–2.44; P = 0.554; q = 0.87)

Receiver operator curve analyses

Adding selected biomarkers to the ASCVD risk score did not significantly improve discrimination for CAD in the overall cohort or within HIV strata **(**Fig. 4**).** In the total cohort, the AUC was 0.696 for ASCVD alone, 0.676 after adding FABP2 (ΔAUC, − 0.021; P = 0.668), and 0.710 after adding sCD163 (ΔAUC, 0.014; P = 0.818). Similar findings were seen in models stratified by HIV serostatus.

Legend: Areas under the curve (AUCs) are shown for ASCVD risk alone and with FABP2 or sCD163, overall and by HIV status. ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; FABP2, fatty acid–binding protein 2; PWH, people with HIV; PWOH, people without HIV; sCD163, soluble CD163.

Discussion

In this study of older adults with and without HIV in rural Uganda, circulating inflammatory biomarkers were generally not associated with prevalent CAD. Although higher sCD163 was inversely associated with CAD in adjusted models, this unexpected finding was not consistent across HIV strata, and sCD163 did not improve discrimination for CAD beyond the atherosclerotic cardiovascular disease risk score. Taken together, our findings suggest a diminished strength of association between systemic and CAD risk in this setting, and that inflammatory biomarkers may have reduced predictive value in identifying CAD.

Chronic inflammation is implicated in the development of atherosclerosis through immune activation, endothelial dysfunction, and plaque progression (27–29). In large general-population studies in the Global North, inflammatory biomarkers such as C-reactive protein have shown modest associations (i.e., 30–50% increased risk with each SD increase) with coronary heart disease after adjustment for conventional risk factors (24). Among PWH, stronger associations have been reported in selected cohorts, including studies linking inflammatory markers with cardiovascular events or subclinical coronary atherosclerosis (22). Our results offer evidence that this strength of association may not pertain to all global populations. Notably, evidence from the United States suggests that both biomarker levels and biomarker–disease relationships vary across racial and ethnic groups (17, 18). For example,

multiethnic cohort data suggest that the prognostic value of novel biomarkers for future cardiovascular events varies by ethnicity, while studies of cardiovascular biomarker profiles have shown systematic racial differences in inflammatory and vascular biomarkers. These observations reinforce the need for population-specific evidence on biomarker–CVD associations and caution against direct extrapolation from high-income cohorts to rural African settings.

The largely null findings in our study may also reflect limited statistical power afforded by the low prevalence of CAD in the cohort. In Uganda, emerging data suggest a relatively low population prevalence of coronary atherosclerosis, which is observed despite a substantial burden of conventional risk factors, and that relationships between inflammatory markers and CAD may differ from those reported elsewhere (19, 20, 30). Alternatively, systemic inflammation may contribute less strongly to coronary atherosclerosis in the Ugandan population than in high-income settings, or circulating biomarkers may poorly capture localized arterial-wall inflammation and plaque biology (29).

The inverse association between sCD163 and CAD was unexpected because prior studies have generally linked higher sCD163 levels with greater cardiovascular risk, particularly in the context of HIV-related monocyte–macrophage activation (7, 23, 31). At the same time, the broader cardiovascular literature suggests that sCD163 may not relate uniformly to all cardiovascular phenotypes. In the Cardiovascular Health Study, sCD163 showed clearer associations with all-cause mortality, cardiovascular mortality, and incident heart failure than with CAD, for which the association attenuated after fuller adjustment (18). Our study assessed prevalent CAD, but not cardiovascular events or mortality. Thus, the observed inverse association may therefore suggest that sCD163 may reflect broader monocyte–macrophage activation and downstream cardiovascular vulnerability more strongly than prevalent structural coronary plaque alone.

Prior Ugandan studies have suggested that sex may modify associations between inflammation and CAD. In a Kampala cohort enriched for cardiovascular risk factors, Shakil et al. found that higher sCD163 predicted subsequent CAD more strongly among women than men (20). In contrast, we found no evidence that sex modified the association between sCD163 and CAD. The inverse association was directionally similar among men and women, although the estimate among women was imprecise because of the small number of events. Differences in study population, urban versus rural setting, cardiovascular risk profile, outcome timing, and statistical power may partly explain the divergent findings. Larger longitudinal studies are needed to determine whether sex-specific inflammatory pathways contribute differently to CAD across African populations.

Our findings also help contextualize the relative contribution of inflammatory biomarkers versus traditional cardiovascular risk factors. In this cohort, adding biomarkers to the ASCVD risk score did not meaningfully improve discrimination in either HIV stratum. This pattern supports the conclusion that established cardiovascular risk factors remain more useful than inflammatory markers for identifying imaging-defined CAD in older Ugandan adults (19, 32–35). More broadly, the absence of strong and consistent biomarker associations may reflect the limited ability of circulating markers to capture

localized vascular inflammation, as well as the modifying influence of aging, background inflammatory exposures, and non-cardiovascular sources of systemic inflammation in this setting (8, 36–38).

The findings should be interpreted considering several limitations. First, the cross-sectional design precludes conclusions about temporality or causal relationships between inflammation and CAD prevalence. Second, the relatively small number of CAD events reduced statistical power, particularly in HIV-stratified analyses. Although several confidence intervals were wide enough that modest-to-moderate associations cannot be excluded, most point estimates were close to the null and were broadly consistent in that direction, suggesting that any true relationships in this cohort are unlikely to be large. Additionally, the small number of CAD events among women limited precision in sex-stratified analyses and reduced our ability to detect potentially meaningful biomarker-by-sex interactions. Third, biomarker-specific missingness reduced analytic sample sizes for some models. Fourth, circulating biomarkers were measured at a single time point and may not reflect cumulative or time-varying inflammatory exposure. Fifth, because the study focused on imaging-defined subclinical CAD rather than clinical cardiovascular events, the findings may not generalize to myocardial infarction, stroke, or cardiovascular mortality.

Limitations notwithstanding, our study has several strengths. It used coronary computed tomography imaging to objectively assess subclinical CAD and included both people living with HIV and HIV-negative participants from the same setting. The evaluation of multiple circulating biomarkers and derived inflammatory indices provided a broad assessment of systemic inflammation, and the use of Firth penalized logistic regression reduced small-sample bias in the setting of relatively few CAD events.

Conclusions

Inflammatory biomarkers showed limited associations with imaging-defined CAD in this Ugandan cohort. sCD163 was the only biomarker with an association, but the inverse direction was unexpected, may reflect population-specific biology or false discovery, and did not improve discrimination beyond conventional cardiovascular risk assessment. These findings support continued emphasis on established cardiovascular risk assessment and highlight the need for more thorough pathophysiologic discovery about CAD risk in African populations with and without HIV.

Abbreviations

ASCVD
atherosclerotic cardiovascular disease
AUC
area under the curve
BMI
body mass index
CAD

coronary artery disease
CAD-RADS
Coronary Artery Disease–Reporting and Data System
CBC
complete blood count
CCTA
coronary computed tomography angiography
CI
confidence interval
CRP
C-reactive protein
CT
computed tomography
CVD
cardiovascular disease
DBP
diastolic blood pressure
ECG
electrocardiogram
ELISA
enzyme-linked immunosorbent assay
FABP2
fatty acid–binding protein 2
HbA1c
glycated hemoglobin
HDL
high-density lipoprotein cholesterol
HIV
human immunodeficiency virus
hs-CRP
high-sensitivity C-reactive protein
LDL
low-density lipoprotein cholesterol
LMR
lymphocyte-to-monocyte ratio
MHR
monocyte-to–high-density lipoprotein cholesterol ratio
NLR
neutrophil-to-lymphocyte ratio
OR

odds ratio
PIV
pan-immune-inflammation value
PLR
platelet-to-lymphocyte ratio
PWH
people with HIV
PWOH
people without HIV
ROC
receiver-operating-characteristic
SBP
systolic blood pressure
sCD163
soluble CD163
SII
systemic immune-inflammation index
SIRI
systemic inflammation response index.

Declarations

Ethics approval and consent to participate
The parent study was approved by institutional review boards in Uganda and the United States. Written informed consent was obtained from all participants before enrollment. The current analysis was conducted on de-identified data collected under the approved parent protocol. Additionally, the current study received approval from Mbarara University of Science and Technology Research Ethics Committee (MUST-REC).

Clinical trial registration

Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reasonable request and subject to applicable ethical and institutional approvals.

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
RM and MJS conceived the analysis. RM performed the statistical analysis, interpreted the data, and drafted the initial manuscript. MJS provided overall scientific supervision and contributed to the analytic approach and interpretation of findings. PBK, PK, AM, GE, CTL, BG, PB, RN, GM, FA, ET, RFG, ZR, MR, VT, AT, EP, MA, AO, SA, and SO contributed to the parent study design, data generation, clinical or imaging interpretation, data management, or contextual interpretation of the findings. PBK, PK, AM, SA, SO, and MJS critically revised the manuscript for important intellectual content. All authors reviewed and approved the final manuscript.

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