

Cystatin C based estimation of glomerular filtration rate and association with atherosclerosis imaging markers in people living with HIV

Running head: HIV, Cystatin C, and Atherosclerosis Imaging

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Abstract:

Introduction: Reduced estimated glomerular filtration rate (eGFR) is associated with increased risk of cardiovascular disease among people living with HIV (PLWH). It is unclear whether eGFR equations incorporating Cystatin C (CysC) measurements are more predictive of preclinical CVD than those using only creatinine (Cr).

Objectives: The study aimed to determine which of the three Chronic Kidney Disease Epidemiology (CKD-EPI) eGFR equations is most associated with carotid intima media thickness (CIMT) and coronary artery calcium (CAC) score.

Methods: This cross-sectional analysis of pooled data from three large cohorts compared the associations between the three CKD-EPI eGFR equations (Cr, CysC, and Cr-CysC) with CIMT and CAC score using multivariable regression analysis. eGFR and CIMT were analyzed as continuous variables. CAC scores were analyzed as a binary variable (detectable calcification versus nondetectable) and as a log₁₀ Agatston score in those with detectable CAC.

Results: 1487 participants were included, and of these 910 (562 HIV+, 348 HIV-) had CIMT measurements and 366 (296 HIV+, 70 HIV-) had CAC measurements available. In HIV- participants, GFR estimated by any CKD-EPI equation did not significantly correlate with CIMT or CAC scores. When PLWH were analyzed separately including HIV-specific factors, only GFR estimated using Cr-Cys C correlated with CIMT [$\beta = -0.90$, 95% CI (-1.67, -0.13) μm ; $p = 0.023$]. Similarly, eGFR correlated with Agatston scores only when using cystatin C-based

eGFR [$\beta = -8.63$, 95% CI (-16.49,-0.77) HU; $p=0.034$]. Associations between other eGFR formulas and CAC did not reach statistical significance.

Conclusion: In PLWH, preclinical atherosclerosis may be more closely correlated with eGFR using formulae that incorporate CysC measurements than Cr alone.

Key words: HIV-1; Cystatin C; Carotid Intima Media Thickness; Coronary Artery Calcium; Cardiovascular disease; Glomerular Filtration Rate

Introduction

Reduced estimated glomerular filtration rate (eGFR) is associated with an increased risk of cardiovascular disease (CVD) in both the general population^[1, 2] and people living with HIV (PLWH)^[3-5]. GFR estimating equations incorporating serum cystatin C, compared to those using solely serum creatinine, are more predictive of cardiovascular events and overall mortality in the general population^[6] and of overall mortality in PLWH^[4, 7-10]. We sought to determine whether cystatin C-based or creatinine-based estimates of GFR were more strongly associated with two measures of subclinical cardiovascular disease, which are predictors of cardiovascular events, namely carotid intima media thickness (CIMT) and coronary artery calcium (CAC)^[11-17]

Methods

We conducted a cross sectional analysis of data pooled from three large observational cohorts of PLWH and HIV- uninfected (HIV-) controls [Veterans Aging Cohort Study (VACS), Multicenter AIDS Cohort Study (MACS), and Hawaii Aging with HIV-1 Cohort (HA)]. We used multivariable regression analysis to evaluate correlations between GFR with both CIMT

(ultrasound measured at the right distal common carotid artery) and CAC scores measured by CT scanning. We performed these analyses using each of three CKD-EPI eGFR equations [creatinine (Cr), cystatin C (CysC), and both creatinine and cystatin C (Cr-CysC)]^[18, 19]. Serum CysC was quantified centrally using N Latex Cystatin C kit per manufacturer instructions (Seimens, Eschborn, Germany). Our models included the entire pooled cohort and included an interaction term between HIV serostatus and eGFR. Covariates in all models included demographic factors (age, sex, race/ethnicity) and CVD and kidney disease risk factors (systolic and diastolic blood pressure, history of diabetes, total cholesterol, LDL-C, HDL-C, triglycerides, smoking status, body mass index, hepatitis C serostatus). We also constructed models in PLWH alone and included HIV-specific factors (CD4+ T cell count, HIV-1 RNA level, and history of antiretroviral medication use). CIMT, CAC, and CysC were centrally measured as previously described^[20-22]; serum Cr was measured locally. eGFR and CIMT were analyzed as continuous variables. CAC scores were analyzed as a continuous variable using log₁₀Agatston score in persons with detectable CAC. Statistical significance was defined as P<0.05.

Results

We included 1487 participants (945 HIV+, 542 HIV-). Of these 910 (562 HIV+, 348 HIV-) and 366 (296 HIV+, 70 HIV-) had CIMT and CAC measurements available, respectively (Supplementary Table 1, <http://links.lww.com/QAI/B519>). Among persons with CIMT measurements, 96.3% were male, 22.5% were Black, 11.9% Hispanic, 57.9% White, and 7.7% Asian. There were 4.3-5.4% with eGFR <60 mL/min/1.73m² and 25.1-52.3% had eGFR <90 mL/min/1.73m², depending on the eGFR formula used. Mean (SD) CIMT was 0.79 (0.15) mm (Supplementary Table 1, <http://links.lww.com/QAI/B519>).

Among persons with CAC measurements, 94% were male, 47% were Black, 9.6% were Hispanic, 31.5% were White, and 11.8% were Asian. There were 4.8-5.9% with eGFR <60 mL/min/1.73m² and 27-52.8% had eGFR <90 mL/min/1.73m², depending on the eGFR formula used. Of the 366 with CAC measurements, 176 (48.1%) had detectable CAC, with a mean (SD) log₁₀Agatston score of 1.87 (0.79) (Supplementary table 1, <http://links.lww.com/QAI/B519>).

In the overall cohort including both PLWH and HIV- participants, neither creatinine nor cystatin C-based eGFR were associated with greater CIMT (Table 1). Of note, there was an interaction between HIV status and Cr based eGFR's relationship with CIMT (β (95% CI) = -1.32 (-2.49,-0.15), P=0.027). When PLWH were analyzed separately including HIV-specific factors, eGFR using Cr-Cys C model correlated with greater CIMT. In PLWH, each 10 mL/min/1.73m² lower in eGFR by Cr-CysC was associated with a 9.0 μ m (95% CI, -16.7,-1.3 μ m; P=0.023) greater CIMT. Associations with other eGFR formulas did not reach statistical significance.

Similarly, neither creatinine nor cystatin C based estimates of GFR were associated with greater Agatston scores in the cohort regardless of HIV serostatus (Table 2). However, when PLWH were analyzed separately including HIV-specific factors, eGFR correlated with higher Agatston scores only when using cystatin C-based eGFR. Each 10 mL/min/1.73m² decrease in CysC-eGFR was associated with a 0.086 higher log₁₀Agatston score (95% CI .077, 0.165; P=0.034). Associations between other eGFR formulas and CAC did not reach statistical significance. None of the GFR estimates were associated with CAC when analyzed as a binary variable (detectable vs non-detectable calcification), regardless of HIV serostatus.

Discussions

In this large and diverse cohort, estimates of GFR that incorporated CysC were more significantly correlated with CIMT measurements and Agatston scores in PLWH than GFR estimates without CysC. In PLWH, eGFR was inversely correlated to CIMT using Cr-CysC, but not with Cr or CysC; eGFR was inversely correlated with CAC Agatston scores using CysC but not with Cr or Cr-CysC. This suggests that GFR estimating formulae incorporating cystatin C may be more useful to identify PLWH with subclinical CVD who are in greater need of aggressive CVD risk reduction. These results are consistent with several studies suggesting that cystatin C-based eGFR is more predictive of both CVD and mortality than Cr in PLWH^[4, 8, 9, 23]. One study reported that CysC eGFR had the strongest association with cardiovascular events of the three CKD-EPI equations among PLWH^[8]. To date, there has not been a study demonstrated that CysC-based eGFR in PLWH is more closely associated with greater CAC or CIMT than Cr-based eGFR. A recent study using CT angiography found a correlation between Cr-based eGFR and calcified coronary plaque and Agatston score in PLWH, but not in HIV- controls^[5]. In our analysis, creatinine based eGFR did not correlate with higher Agatston scores, but cystatin C based eGFR did. This may be explained in part by different methodology of Agatston score measurement or differences in study population (their cohort was modestly younger and included more women).

Of note, our analysis did not consistently reveal a link between HIV infection itself and greater CIMT or CAC. Similarly, a recent large study suggests that HIV's association with CIMT may be age dependent, with middle-aged patients showing little association between HIV and CIMT^[24]. Other studies have examined CIMT's association with HIV and some reported higher CIMT values among PLWH, while others found such an association only in certain

subgroups of PLWH^[15, 25, 26]. The addition of kidney function estimates in our models may also have minimized the relationship between HIV seropositivity and these imaging markers.

Strengths of our study include having large samples of both PLWH and HIV- participants, use of standardized centrally-measured plasma cystatin C, CIMT, and CAC scores, and adjustment for other factors known to contribute to development of both renal and cardiovascular disease.

However, our study is limited by having a predominantly male population with few having an eGFR <60 mL/min/1.73m². We did not have data on antiretroviral, blood pressure, and lipid-lowering medications, which may have confounding effects on kidney function. Finally, we could not assess causality in this cross-sectional analysis.

In conclusion, investigators studying the interplay between CVD and renal disease in PLWH should consider utilizing eGFR formulae that incorporate CysC since these may correlate more significantly with atherosclerosis in PLWH.

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Table 1. Relationships between eGFR (using 3 CKD-EPI equations) and CIMT in HIV-positive and HIV-negative Individuals.

	CIMT					
	Cr Model		CysC Model		Cr-CysC Model	
	β (95% CI) ^a	P-value	β (95% CI) ^a	P-value	β (95% CI) ^a	P-value
Overall cohort						
HIV status (+/-)	126.33 (12.95, 239.72)	0.029	11.91 (-121.35, 145.16)	0.861	79.78 (-59.37, 218.93)	0.262
HIV- eGFR (mL/min/1.73m ²)	0.74 (-0.27, 1.76)	0.152	-0.40 (-1.47, 0.67)	0.465	0.06 (-1.12, 1.24)	0.923
HIV+ eGFR (mL/min/1.73m ²)	-0.58 (-1.27, 0.11)	0.099	-0.61 (-1.23, 0.01)	0.055	-0.78 (-1.48, -0.08)	0.029
HIV*eGFR interaction	-1.32 (-2.49, -0.15)	0.027	-0.21 (-1.40, 0.98)	0.729	-0.84 (-2.15, 0.48)	0.213
HIV+ only						
eGFR (mL/min/1.73m ²)	-0.74 (-1.50, 0.01)	0.055	-0.64 (-1.33, 0.05)	0.069	-0.90 (-1.67, -0.13)	0.023

Abbreviations: CIMT, Carotid Intima Media Thickness; Cr, Creatinine; CysC, Cystatin C; eGFR, estimated glomerular filtration rate based on CKD-EPI equations using either Creatinine, Cystatin C, or both

^aIn the overall cohort, the β -coefficients are from a multivariable regression model including eGFR (per 1 mL/min/1.73²), HIV status (positive vs. negative), and the interaction between eGFR and HIV status on the level of CIMT (in μ m). Variables included in all models include age, race/ethnicity, sex, smoking status, body mass index, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, total cholesterol, triglycerides, systolic and diastolic blood pressures, history of diabetes, and Hepatitis C serostatus. Similar regression models were then constructed to assess the relationships between eGFR and CIMT using just HIV+ participants including several HIV-specific variables such as history of antiretroviral use, CD4 cell count and HIV-1 RNA level.

Table 2. Relationships between eGFR (using 3 CKD-EPI equations) and Coronary Artery Calcification in HIV-positive and HIV-negative Individuals.

	CAC (+/-)					
	Cr Model		CysC Model		Cr-CysC Model	
	β (95% CI) ^a	P-value	β (95% CI) ^a	P-value	β (95% CI) ^a	P-value
Overall cohort						
HIV status (+/-)	0.077 (0.001,8.458)	0.286	0.025 (0.000,8.386)	0.215	0.032 (0.000,8.936)	0.233
HIV- eGFR (mL/min/1.73m ²)	0.986 (0.945,1.028)	0.5	0.968 (0.921,1.017)	0.197	0.973 (0.927,1.021)	0.268
HIV+ eGFR (mL/min/1.73m ²)	1.003 (0.986,1.020)	0.729	0.994 (0.978,1.010)	0.468	0.997 (0.979,1.015)	0.734
HIV*eGFR interaction	1.018 (0.973,1.064)	0.443	1.027 (0.976,1.082)	0.307	1.025 (0.974,1.078)	0.349
HIV+ only						
eGFR (mL/min/1.73m ²)	1.003 (0.985,1.021)	0.758	0.992 (0.975,1.009)	0.364	0.996 (0.978,1.015)	0.699
	CAC log ₁₀ Agat					
	Cr Model		CysC Model		Cr-CysC Model	
	β (95% CI) ^a	P-value	β (95% CI) ^a	P-value	β (95% CI) ^a	P-value
Overall cohort						
HIV status (+/-)	169.41 (-1925.19, 2264.0)	0.874	443.47 (-2078.79, 2965.74)	0.731	392.28 (-2235.71,3020.26)	0.770
HIV- eGFR (mL/min/1.73m ²)	4.18 (-13.83,22.18)	0.650	-8.57 (-27.94,10.79)	0.388	-3.47 (-23.55,16.62)	0.736
HIV+ eGFR (mL/min/1.73m ²)	3.82 (-4.52,12.15)	0.371	-9.72 (-17.46,-1.97)	0.016	-3.64 (-12.49,5.20)	0.421
HIV*eGFR interaction	-0.36 (-19.56,18.83)	0.971	-1.14 (-21.29,19.00)	0.912	-0.17 (-21.28,20.93)	0.987
HIV+ only						
eGFR (mL/min/1.73m ²)	3.40 (-4.96,11.77)	0.427	-8.63 (-16.49,-0.77)	0.034	-2.83 (-11.78,6.12)	0.537

Abbreviations: Cr, Creatinine; CysC, Cystatin C; eGFR, estimated glomerular filtration rate based on CKD-EPI equations using either Creatinine, Cystatin C, or both; CAC log Agat, Coronary Artery Calcium log₁₀ Agatson score; CAC(+/-), Coronary Artery Calcium detectable/nondetectable.

^aIn the overall cohort, the β -coefficients are from a multivariable regression model including eGFR (per 1 mL/min/1.73²), HIV status (positive vs. negative), and the interaction between eGFR and HIV status on the level of CAC (log₁₀ Agatson score or as detectable vs. nondetectable). Variables included in all models include age, race/ethnicity, sex, smoking status, body mass index, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, total cholesterol, triglycerides, systolic and diastolic blood pressures, history of diabetes, and Hepatitis C serostatus. Similar regression models were then constructed to assess the relationships between eGFR on CAC using just HIV+ participants including several HIV-specific variables such as history of antiretroviral use, CD4 cell count and HIV-1 RNA level.

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