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Biomarkers: Kidney biomarkers predict mortality in patients with HIV disease

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Chronic kidney disease (CKD) is accompanied by significantly increased risk for cardiovascular disease and death in the general population. In a multicenter US cohort of individuals with HIV disease, Choi et al. found that serum cystatin C estimated glomerular filtration rate <60 ml/min/1.73m² and albuminuria each conferred increased mortality risk¹. Taken together, these two markers of CKD accounted for 17% of population-attributable 5-year mortality risk, corresponding to 2.4 deaths/100 HIV persons over 5 years.

In the US and the rest of the developed world, access to combined anti-retroviral therapy (cART) has converted HIV disease, for most individuals, from a rapidly fatal disease to a chronic disease. Similarly, as the HIV epidemic has evolved over the past three decades, the causes of death have changed. Initially, prior to the availability of anti-retroviral therapy, most deaths were due to opportunistic infections and acquired immunodeficiency syndrome (AIDS)-defining cancers. Currently, the major causes of death are similar to those of the general population, including cardiovascular disease and non-AIDS-defining cancers, but these deaths occur at earlier age than in the general population².

HIV disease has been described as a disease of early aging, with many factors that contribute to aging also a part of HIV pathogenesis³. These include inflammation, metabolic syndrome, immunosenescence, genotoxicity, and mitochondrial dysfunction. Biomarkers of inflammation and pro-coagulant activity, and in particular interleukin-6, sCD14 (a marker of monocyte/macrophage inflammation) and D-dimer (a marker of fibrinolysis, and this indirectly a marker of coagulation) are elevated in subjects with HIV disease⁴. Inflammation may reflect persistent immune activation, which may compromise immune reconstitution, and which may promote end-organ damage⁵.

Increased cardiovascular risk in HIV disease is likely due to the interaction of host factors, viral factors and ant-viral therapy⁶. Uncontrolled HIV infection, acting via immune activation, is associated with macrophage activation and elevated inflammatory markers, including C-reactive protein (CRP). While cART suppresses viral burden, it also promotes cardiovascular risk. This is mediated by elevated plasma lipids and insulin resistance (protease inhibitors) and by unknown mechanisms (abacavir, a nucleoside analog reverse transcriptase inhibitor).

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Biomarkers of chronic kidney disease include serum creatinine and cystatin C, each of which can be used to derive an estimated glomerular filtration rate (eGFR), and albuminuria. Among these measures, elevated serum cystatin C (and $\text{eGFR}_{\text{SCysC}}$) and albuminuria are particularly effective at identifying populations that are at increased risk for cardiovascular events in various populations. Serum creatinine is less predictive of cardiovascular events, perhaps due to the confounding effects of low muscle mass. Thus elevated serum cystatin C predicts cardiovascular mortality among the elderly Swedes⁷, CHF in the Physicians Health Study⁸, and cardiovascular events and mortality in the Cardiovascular Health Study⁹. Similarly, serum cystatin C is a powerful predictor of mortality in the general CKD population as shown recently by Peralta and colleagues using data from nearly 12000 subjects in the Multi-ethnic Study of Atherosclerosis and Cardiovascular Health Study¹⁰. In these studies, $\text{eGFR}_{\text{SCysC}}$ identified fewer individuals with CKD but the individuals with CKD were at significantly higher risk for CVD compared to individuals identified by eGFR_{SCr} .

At least three studies have previously examined the impact of CKD on cardiovascular disease or mortality in HIV disease. Using data from the Women's Interagency Health Study, Szczech et al. found that proteinuria and serum creatinine predicted mortality¹¹, and Wyatt et al extended the association to microalbuminuria¹². Recently, Choi et al. reported that albuminuria and reduced eGFR predicted cardiovascular events in study within the Veterans Administration population¹³.

In the study by Choi et al., baseline serum cystatin C and albuminuria each, and combined, predict 5-year mortality in 922 subjects with HIV disease who participated in the FRAM (Fat Redistribution and Metabolic Disease) study¹. This is the first study to examine the relationship between cystatin C and mortality in HIV disease. The authors used multivariable analysis, using known predictors of HIV-associated mortality and of cardiovascular mortality, including the inflammatory markers C-reactive protein and fibrinogen. At baseline, the fraction of the study population with $\text{eGFR} < 60 \text{ ml/min/1.73m}^2$ was higher with cystatin C, using the CKD-EPI equation (11%) than with creatinine using the MDRD equation (5%). Albuminuria, defined as a dipstick reading of 1+ or albumin/creatinine ratio $> 30 \text{ mg/g}$, was present in 22% of subjects.

Importantly, $\text{eGFR}_{\text{SCysC}} < 60 \text{ ml/min/1.73m}^2$ was more predictive of 5-year mortality than was eGFR_{SCr} . The authors adjusted for demographic variables, clinical variables (medication use, waist circumference, lean body mass, diabetes, blood pressure, high density lipoprotein), viral factors (CD4 counts, HIV RNA levels, AIDS, and hepatitis C) and inflammatory markers (serum CRP, fibrinogen). After adjustment, the odds ratio for five-year mortality increased 1.01 (95% CI 0.92, 1.12) for each 10 ml decrease in eGFR_{SCr} , and 1.41 (1.03, 1.27) for each 10 ml decrease in $\text{eGFR}_{\text{SCysC}}$. Put in more clinically meaningful terms, the odds ratio for 5-year mortality was 0.98 (0.42, 2.26) for those with $\text{eGFR}_{\text{SCr}} < 60 \text{ ml/min/1.73m}^2$, 1.86 (1.09, 3.19) for those with $\text{eGFR}_{\text{SCysC}} < 60 \text{ ml/min/1.73m}^2$, and 1.91 (1.15, 3.19) for those with albuminuria.

While the confidence intervals are broad due to the relatively modest sub-group sizes, the findings are striking. The authors estimate that the presence of either $\text{eGFR}_{\text{SCysC}} < 60$

ml/min/1.73m² or albuminuria is associated with a death rate of 2.4 deaths/100 HIV-infected persons over 5 years. As shown in Figure 1, renal dysfunction accounts for a substantial fraction (17%) of HIV mortality in a contemporary HIV population with extensive exposure to cART.

The study has several limitations. As the authors note, vital status and dates of death was not available for all subjects and they used appropriate statistical approaches to address this problem. Causes of death were not available, and so the role of cardiovascular disease could not be determined. Finally, despite adjustment for certain known inflammatory markers (CRP and fibrinogen), it is unclear whether elevated serum cystatin C retains some degree of association with a pro-inflammatory state as well as serving as a marker of renal function. The superiority of GFR_{SCysC} over eGFR_{SCr} in predicting mortality could be due to a residual association between serum cystatin C and inflammation; a tendency of eGFR_{SCr} to underestimate true GFR, perhaps due to lower muscle mass in HIV disease leading lower serum creatinine for any particular level of GFR; or to other unknown factors.

What do these findings mean for the practicing HIV clinician? Before firm conclusions can be drawn, these findings must be replicated in additional HIV disease populations, in the US and elsewhere. Further, the relationship between CKD and mortality in HIV disease must be further elucidated and the clinical benefit of interventions must be demonstrated, but it is clear from the general population that CKD is a major risk factor for cardiovascular disease¹⁴. Further, the cost of regular measurements of cystatin C must be considered. Nevertheless, if the findings of Choi et al. are confirmed, it may be that periodic determination of albuminuria and eGFR_{SCysC} in HIV disease will help to identify individuals in whom control of modifiable cardiovascular disease risk factors should be a high priority.

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Figure 1. Contribution of CKD markers to population-attributable 5-year mortality risk. Population level risk, adjusted for relevant variables, for 5 year mortality is shown for those with eGFR_{CysC} <60 ml/min per 1.73m², albuminuria, or both parameters. Modified, with permission, from Choi et al, AJKD, 2010.