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Ambulatory Urine Biomarkers Associations with AKI and Hospitalization in People with HIV: Predictors of Acute Renal Injury Study (PARIS)

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Abstract

Background: People living with HIV (PLWH) generally have worse ambulatory levels of kidney injury biomarkers and excess risk of acute kidney injury (AKI) compared to persons without HIV. We evaluated whether ambulatory measures of subclinical kidney injury among PLWH are associated with subsequent AKI.

Methods: In the Predictors of Acute Renal Injury Study (PARIS), which enrolled 468 PLWH from April 2016 to August 2019, we measured 10 urine biomarkers of kidney health (albumin, a1m, b2M, NGAL, IL18, KIM-1, EGF, UMOD, MCP-1, YKL40) at baseline and annually during follow-up. Using multivariable Cox regression models, we evaluated baseline and time-updated biomarker associations with the primary outcome of AKI (≥0.3 mg/dL or ≥1.5-times increase in serum creatinine from baseline) and secondary outcome of all-cause hospitalization.

Results: At baseline, the mean age was 53 years old, and 45% self-identified as female. In time-updated models adjusting for sociodemographic factors, comorbidities, albuminuria, eGFR, and HIV-associated factors, higher KIM-1 (HR=1.30 per 2-fold higher; 95% CI 1.03–1.63) and NGAL

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concentrations (HR=1.24, 95% CI 1.06–1.44) were associated with higher risk of hospitalized AKI. Additionally, in multivariable, time-updated models, higher levels of KIM-1 (HR=1.19, 95% CI 1.00, 1.41), NGAL (HR=1.13, 95% CI 1.01–1.26), and MCP-1 (HR=1.20, 95% CI 1.00, 1.45) were associated with higher risk of hospitalization.

Conclusions: Urine biomarkers of kidney tubular injury, such as KIM-1 and NGAL, are strongly associated with AKI among PLWH, and may hold potential for risk stratification of future AKI.

Keywords

HIV; Acute Kidney Injury; All-cause hospitalization; Ambulatory kidney biomarkers; Kidney tubular injury

Introduction:

Acute kidney injury (AKI) is extremely common among persons living with HIV (PLWH) [1], affecting up to 1 in 6 hospitalized patients [2]. In addition, AKI among PLWH is associated with higher risk of cardiovascular disease, end-stage kidney disease (ESKD), and death [2, 3]. The traditional measure of kidney function, serum creatinine concentration, is relatively insensitive and non-specific [4, 5]; it does not localize the site of kidney injury and may only capture AKI once substantial kidney function has been lost [6].

Given the above limitations of serum creatinine, recent investigations have sought alternative biomarkers for assessing kidney health. In addition to albuminuria, a marker of glomerular/endothelial injury – several urine biomarkers which capture unique dimensions of kidney tubule health have been identified; 1) tubular dysfunction – alpha 1 microglobulin (a1m) and beta-2 microglobulin (b2M); 2) tubular injury – interleukin 18 (IL18), kidney injury molecule 1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL); 3) tubular synthetic function and resilience - epidermal growth factor (EGF) and uromodulin (UMOD); and 4) tubulointerstitial inflammation and fibrosis – monocyte chemoattractant protein 1 (MCP-1) and chitinase-3-like protein 1 (YKL40). Studies across different clinical settings have demonstrated that these urine biomarkers of tubule health can effectively prognosticate adverse outcomes, independent of serum creatinine and albuminuria, including post-operative AKI, progression of AKI, long-term mortality, and chronic kidney disease (CKD) onset and progression [7–12].

Among ambulatory PLWH, these urine biomarkers have been shown to capture antiretroviral drug-related nephrotoxicity [13–15]. They are also elevated in PLWH compared to non-infected persons, with higher values associated with faster longitudinal kidney function decline [16, 17]. These results suggest that PLWH have ongoing subclinical kidney damage that is not sufficiently captured by serum creatinine. However, whether or not this subclinical kidney damage in the ambulatory setting is associated with higher risk of hospitalized AKI or hospitalization remains unknown.

To answer this question, we designed and implemented the Predictors of Acute Renal Injury Study (PARIS) cohort of PLWH, which includes both ambulatory and in-hospital

assessments. We hypothesized that worse kidney tubule health, as depicted by urine biomarker levels in the ambulatory setting, is associated with risk of incident hospitalization and hospitalized AKI, independent of traditional kidney risk factors.

Methods:

Study Population and Design:

The PARIS Cohort was established to determine associations of ambulatory kidney damage with AKI and related adverse health outcomes in PLWH. Details of the study have been previously described [18]. In brief, PARIS prospectively enrolled and followed participants living with HIV with integration of standardized interviews, biosamples at regular intervals, and electronic medical record (EMR) data acquisition from the Johns Hopkins Health System. The study recruited from the ambulatory setting within the Johns Hopkins Hospital HIV Clinic in Baltimore, Maryland from April 2016 through August 2019. To be eligible for enrollment, participants had to meet the following criteria: 1) known to be living with HIV; 2) age ≥18 years; 3) received HIV care through the HIV Clinic at Johns Hopkins; and 4) did not have AKI within the preceding 6 months. Individuals were excluded if they: 1) resided in a hospice, skilled nursing facility, or prison; 2) had health conditions that would interfere with study participation (e.g. cognitive impairment or active psychotic illness); 3) received chronic renal replacement therapy or had estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m^2; 4) were pregnant; 5) had undergone prior solid organ transplantation; 6) planned to move out of the area within the next year; or 7) did not speak English. Informed consent was obtained from all participants. The respective institutional review boards of the University of California, San Francisco and Johns Hopkins University approved this study.

At the baseline visit, standardized interviews were conducted to obtain contact information, family history of kidney disease, co-morbid conditions, medication use including over-the-counter medications, and illicit drug use. Blood and urine samples were collected at baseline and annually in all participants. Those who were hospitalized and who developed hospitalized clinical AKI were identified by serum creatinine derived from the Johns Hopkins EMR and laboratory data systems, with data obtained on all participants from study enrollment to March 1, 2020.

A total of 475 participants were enrolled in PARIS; the present study included 468 participants who had at least one ambulatory visit with urine biomarkers of kidney health.

Urine biomarkers of kidney health measurements

Clean catch urine specimens were collected prospectively at baseline and at each annual study visit and processed immediately into 1-mL aliquots of urine supernatant. Urine samples were then stored at −80^{o} C until biomarker measurements were performed, with no freeze-thaw cycles.

The predictors of interest in this study comprised ten urine biomarkers of kidney health at baseline and at annual ambulatory study visits. Biomarkers of interest included those that conceptually reflect [19–21] 1) glomerular/endothelial injury – albumin; 2) tubular dysfunction – alpha 1 microglobulin (a1m) and beta-2 microglobulin (b2M); 3) tubular

injury – neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18 (IL-18), and kidney injury molecule 1 (KIM-1); 4) tubular synthetic function and resilience - epidermal growth factor (EGF) and uromodulin (UMOD); 5) tubulointerstitial inflammation and fibrosis – monocyte chemoattractant protein 1 (MCP-1) and chitinase-3-like protein 1 (YKL-40). Urine creatinine was also measured using the Creatinine Parameter Assay Kit (RnD Systems, Minneapolis, MN).

With the exceptions of a1m, which was measured using a commercial assay (Siemens BN II Nephelometer, Munich, Germany), and urine creatinine, all urine biomarkers were measured using multiplex immunoassays from Meso Scale Discovery (MSD, Rockville, MD). Inter-assay coefficients of variation (CVs) ranged from 2.3–15.5% for all biomarkers (Supplemental Table 5). All biomarkers were measured at the Kidney Health Research Collaborative Biomarker Laboratory at the San Francisco Veterans Affairs Health Care System, San Francisco, California.

Ascertainment of hospitalized AKI and hospitalization

The primary outcome was incident AKI, defined as the first hospitalization with AKI at The Johns Hopkins Hospital during study follow-up. We defined AKI as ≥0.3 mg/dL increase in serum creatinine or a ≥1.5-fold increase in serum creatinine from baseline in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) AKI criteria [22]. We used previously described methodology to determine baseline serum creatinine [23].

The secondary outcome was first hospitalization for any reason at The Johns Hopkins Hospital during follow-up, irrespective of inpatient AKI.

Covariates

The following covariates reflecting sociodemographic and behavioral factors were included: age, self-reported race, and self-reported gender. Additionally, smoking status and injection drug use at baseline were self-reported as never, past, or current.

The following covariates reflecting comorbid conditions were ascertained through a standardized questionnaire and review of EMR data: hepatitis C virus (HCV) co-infection, history of diabetes mellitus (DM), hypertension, and coronary artery disease (CAD). Serum creatinine was derived from the EMR, using the most recent value preceding the biomarker sample date; $eGFR_{Cr}$ was estimated using the CKD-EPI 2021 equation [24]. The median time between the baseline serum creatinine and biomarker measurements was 20 days (interquartile range [IQR] 1–57 days).

The following covariates reflecting HIV-related factors were included: CD4+ cell count (< or ≥ 200 cell/mm^3) and HIV viral load ((< or ≥ 400 copies/mL) were ascertained from EMR data. History of AIDS (defined as a clinical diagnosis of AIDS or AIDS defining illness) and exposure at baseline to antiretroviral medication classes (nucleoside reverse transcriptase inhibitor [NRTI], non-nucleoside reverse transcriptase inhibitor [NNRTI], integrase strand transfer inhibitors, and protease inhibitor), with separate covariates for specific HIV medications that are known risk factors for AKI (tenofovir disoproxil fumarate, boosted

integrase strand transfer inhibitors, and boosted protease inhibitors), were ascertained through a standardized questionnaire.

Statistical Analysis:

Before embarking on statistical analyses, we first evaluated distributions of the urine biomarkers and covariates. Urine biomarker values were log base 2-transformed (per 2-fold) due to right skewed distributions; values that fell below the lower limit of detection were imputed using the lower limit of detection value divided by 2 or the square root of 2, dependent on the distribution of the biomarker [25]. Biomarkers falling below the lower limit of detection ranged from 0.1% to 7.5% of observations (Supplemental Table 3). For the present study, biomarker measurements were included, up until a participant had the event of interest.

The percentage of missing covariates at the baseline study visit ranged from 1% to 12%. Multiple imputation using fully conditional specification was performed for missing baseline covariates, with 30 imputations generated. The imputation model included sociodemographic factors (smoking status, education, injection drug use, self-reported race/ethnicity, sex), comorbidities (history of HCV, diabetes, hypertension, hyperlipidemia, CAD, angina, myocardial infarction, stroke), HIV related factors (history of AIDS diagnosis or AIDS defining illness, CD4+ cell count, HIV viral load), serum creatinine at baseline, medication exposures (hyperlipidemia medications, non-steroidal anti-inflammatory drugs [NSAIDs]), and both our primary and secondary outcomes of incident AKI and incident hospitalization, respectively.

We summarized baseline demographic and clinical characteristics, overall and stratified by AKI status. The associations of baseline biomarkers (per 2-fold higher) with time to hospitalized AKI and hospitalization were assessed using univariable and staged multivariable Cox proportional hazards regression. The multivariable models were sequentially adjusted for baseline covariates, in two stages: 1) sociodemographic factors and urine creatinine; and 2) comorbid conditions, eGFR, albuminuria, HIV-related factors and antiretroviral medications. The associations of time-updated urine biomarker levels with each outcome were also evaluated, adjusting for the same set of baseline covariates, with the exception of CD4+ count, HIV viral load, eGFR, albuminuria, and urine creatinine which were also time-updated. Given that albuminuria is a clinical standard of kidney disease, we included urine albumin as a covariate in our second model for all other urine biomarkers.

The proportional hazards assumption was evaluated using log(-log survival) plots and Schoenfeld residuals. Individuals were censored at loss-to-follow-up, defined as missing clinical data for >2 years, or death. Additionally, all participants remaining in the study were administratively censored on March 1, 2020, due to the onset of the COVID-19 pandemic in the United States and subsequent changes to hospitalization patterns which affected AKI ascertainment (Supplemental Figure 1).

In additional analyses, we repeated our models for hospitalized AKI using baseline biomarkers indexed to urine creatinine as tertiles using multivariate Cox regression to evaluate for potential nonlinear associations on the log-odds scale. We also performed

sensitivity analyses which used a stricter AKI definition that required a 50% increase in serum creatinine from baseline. Additionally, we conducted a series of analyses which jointly modeled biomarkers which had strong associations with the outcomes, used time-updated biomarker values and adjusted for urine creatinine. Finally, in exploratory analyses to assess which covariates strengthened or weakened the biomarker associations with AKI, we first added covariates one at a time to a base model adjusting for urine creatinine; and separately, we also removed biomarkers one at a time from our fully adjusted model (Supplemental Table 4).

All analyses were completed using StataMP17 (College Station, TX).

Results:

Among 468 participants, 62 (13%) experienced the primary outcome of AKI, and 128 (27%) experienced the secondary outcome of hospitalization, irrespective of AKI. Median observation time was 3.0 years (interquartile range [IQR] 1.9–3.5 years). At baseline, mean age was 53 years, and the cohort was 45% female. Sociodemographic characteristics and medication use at study baseline were largely similar between participants who experienced AKI and those who did not (Table 1). Those who would go on to experience AKI had a higher prevalence of hypertension and diabetes and had lower baseline eGFR.

Association of baseline and time-updated urine biomarkers of kidney health with hospitalized AKI

In sociodemographic adjusted models, each 2-fold higher baseline level of albumin, NGAL, KIM-1, and MCP-1 was significantly associated with higher risk of hospitalized AKI, whereas each 2-fold higher level of EGF and UMOD was associated with lower risk. In analyses additionally adjusted for eGFR, albuminuria, comorbidities, and HIV-associated factors, only NGAL at baseline remained independently associated with AKI. Although KIM-1, EGF, and UMOD no longer reached statistical significance, they retained a moderate directional association with hospitalized AKI (Table 2).

In general, most analyses using time-updated biomarker levels were directionally similar and at least as strong as baseline associations with AKI. In contrast, after multivariable adjustment, time-updated EGF and UMOD levels appeared to have weaker associations with hospitalized AKI compared to their respective baseline values. In sociodemographic adjusted models of time-updated biomarkers, each 2-fold higher level of albumin, b2M, NGAL, KIM-1, and YKL40 was significantly associated with greater risks of hospitalized AKI, and higher time-updated urine EGF levels were associated with lower AKI risk. In the fully adjusted model, only time-updated levels of KIM-1 and NGAL remained independently associated with hospitalized AKI (Table 2).

In sensitivity analyses, associations of baseline biomarkers by tertile were qualitatively similar to the continuous analyses (Figure 1). In analyses using a stricter AKI definition of 1.5-fold increase in serum creatinine alone, only NGAL remained significantly associated with AKI (Supplemental Table 1). Multivariable joint modelling of time-updated KIM-1 (hazard ratio [HR]=1.23, 95% confidence interval [CI] 0.96, 1.57) and NGAL (HR=1.20,

95% CI 1.03, 1.41) showed that these biomarkers were both associated with AKI, independent of one other, although the KIM-1 association was slightly attenuated and no longer statistically significant (Supplemental Table 2).

Associations of baseline and time-updated urine biomarkers of kidney health with incident hospitalization

In sociodemographic adjusted models, each 2-fold higher baseline level of KIM-1, MCP-1, and YKL40 was significantly associated with higher risk of hospitalization. Conversely, higher baseline UMOD was associated with lower incident hospitalization risk. With further adjustment for eGFR, comorbidities, and HIV-associated factors, MCP-1 and YKL40 at baseline remained strongly associated with incident hospitalization (Table 3). KIM-1 and UMOD maintained modest associations with hospitalization but no longer reached statistical significance.

Associations of time-updated levels of urine biomarkers with hospitalization were generally similar to the baseline analyses. In the sociodemographic adjusted models, each 2-fold higher time-updated level of NGAL, KIM-1, MCP-1, and YKL40 was significantly associated with greater risk of incident hospitalization while higher time-updated EGF levels were associated with lower risk of incident hospitalization. In the fully adjusted model, NGAL, KIM-1, and MCP-1 remained significantly associated with incident hospitalization (Table 3).

Discussion

Using the well-characterized, ambulatory population of PLWH enrolled in the PARIS cohort, we showed that both baseline and time-updated levels of ambulatory biomarkers of tubule health are associated with higher risk of hospitalized AKI. These associations were independent of eGFR and albuminuria, which are established predictors of AKI risk and are primarily indicators of glomerular health. Specifically, baseline NGAL and time-updated NGAL and KIM-1 were associated with hospitalized AKI even after adjustment for comorbidities and traditional measures of kidney disease. Similarly, NGAL, KIM-1, and MCP-1 showed strong and independent associations with hospitalization. Herein, we leveraged the PARIS cohort's unique prospective, repeated ambulatory biomarker measures and detailed clinical data on PLWH to characterize the relationships between ambulatory biomarkers and subsequent AKI. These findings suggest that PLWH who have evidence of tubule damage in the ambulatory setting may be predisposed to AKI and hospitalization.

To our knowledge, few studies have evaluated the associations between ambulatory biomarkers of kidney health and AKI. In participants with CKD from the Systolic Blood Pressure Intervention Trial (SPRINT), KIM-1 and NGAL levels at study baseline were modestly associated with subsequent AKI, although these associations were not statistically significant. Higher levels of UMOD showed a strongly protective association with subsequent AKI [26]. A follow-up study within the same participants from SPRINT using exploratory factor analysis found that both the tubule Injury/fibrosis factor (containing KIM-1) and tubule Injury/repair (containing NGAL) were associated with risk for incident AKI [27]. The findings of the present study are generally aligned with the limited literature

that exists on ambulatory biomarkers and AKI. One notable difference is the weaker protective effect of UMOD in the present study, compared to prior studies where UMOD showed a robust association with AKI [26, 27]. This difference may stem from the relatively low burden of prevalent CKD in the PARIS cohort, compared to SPRINT. Additionally, the PARIS cohort was restricted to persons with HIV, and the mechanisms of kidney injury in PLWH, such as nephrotoxicity from antiretrovirals or direct insult from HIV infection, likely differ from those in the general population.

Our findings further extend the importance of subclinical tubular injury (elevated levels of kidney biomarkers that are not reflected by changes in serum creatinine) in the setting of HIV infection. Subclinical tubular injury among PLWH occurs more commonly than in those without HIV [28], possibly due to unique etiologies of kidney injury, such as direct injury from HIV infection and antiretroviral medication toxicity such as tenofovir disoproxil fumarate-induced proximal tubulopathy [13, 29]. These mechanisms may also contribute to the high risk of AKI in PLWH [1]. Prior work has shown that ambulatory subclinical tubular injury in PLWH is associated with long-term clinical kidney outcomes, including incident CKD [30], decline in eGFR [31], and increased all-cause mortality [32]. In the present study, ambulatory measures of tubular injury – KIM-1 and NGAL – were associated with subsequent AKI, independent of eGFR and albuminuria, suggesting that they capture a dimension of kidney health that is overlooked by current clinically used measures. In fact, the clinical measure of kidney damage, urine albumin, had no associations with either AKI or hospitalization risk in this study. In addition to AKI, we found that subclinical tubular injury was associated with all-cause hospitalization, suggesting that perhaps the consequences of subclinical tubular injury might extend beyond the borders of the nephron. In sum, these findings lend support to the growing body of evidence that biomarkers are prognostic of long-term kidney health, specifically risk of AKI. The definition, mechanisms, and implications of subclinical tubular injury warrant further study, particularly among PLWH.

Nonetheless, additional work including standardization of measurements is needed before these ambulatory tubule biomarkers could be considered candidates for routine clinical use. The findings in this study are generally consistent with the signal seen in other biomarker studies, and we add to the growing body of literature supporting eventual measurement standardization and clinical adoption. Future studies should focus on validation of these biomarkers in other cohorts enriched for HIV, determine whether interventions could improve kidney biomarkers, and evaluate whether those improvements could translate to decreased risk of AKI and hospitalization.

Strengths of our study included a well-characterized cohort of PLWH with rich baseline and follow-up clinical data as well as longitudinal measures of urine biomarkers. The present study also has limitations. First, hospitalization and AKI were determined by EMR data from the Johns Hopkins Health System; thus, hospitalizations and/or labs drawn outside of the system would not have been captured. However, almost all of the patients seen in the Johns Hopkins Hospital HIV Clinic are hospitalized at The Johns Hopkins Hospital. Secondly, we do not know the reason for hospitalization or the etiology of AKI, which introduces the potential for residual confounding. Thirdly, given the limited number of

primary events, we were judicious in our selection of covariates, and the results remain subject to residual confounding. Lastly, the PARIS cohort comprised predominantly of Black and African American individuals, limiting the generalizability of the results to other populations.

In conclusion, in this cohort of PLWH, higher levels of ambulatory KIM-1 and NGAL have robust associations with risks of AKI and hospitalization. Ambulatory biomarkers of tubular injury may hold potential for risk stratification of future AKI and hospitalization, among PLWH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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M.L. contributed to study design, analyzed data, and wrote and revised the manuscript. R.S., M.G.S., E.M., and E.V. contributed to study design and data analysis, and revised the manuscript. W.T. analyzed the biomarker samples. C.R.P., C.P.C.V, J.M.M.T., and R.D.P. contributed to study design, oversaw data collection, and revised the manuscript. M.M.E. designed the study, supervised the study including data collection and analysis, and revised the manuscript. All authors read and approved of the final manuscript.

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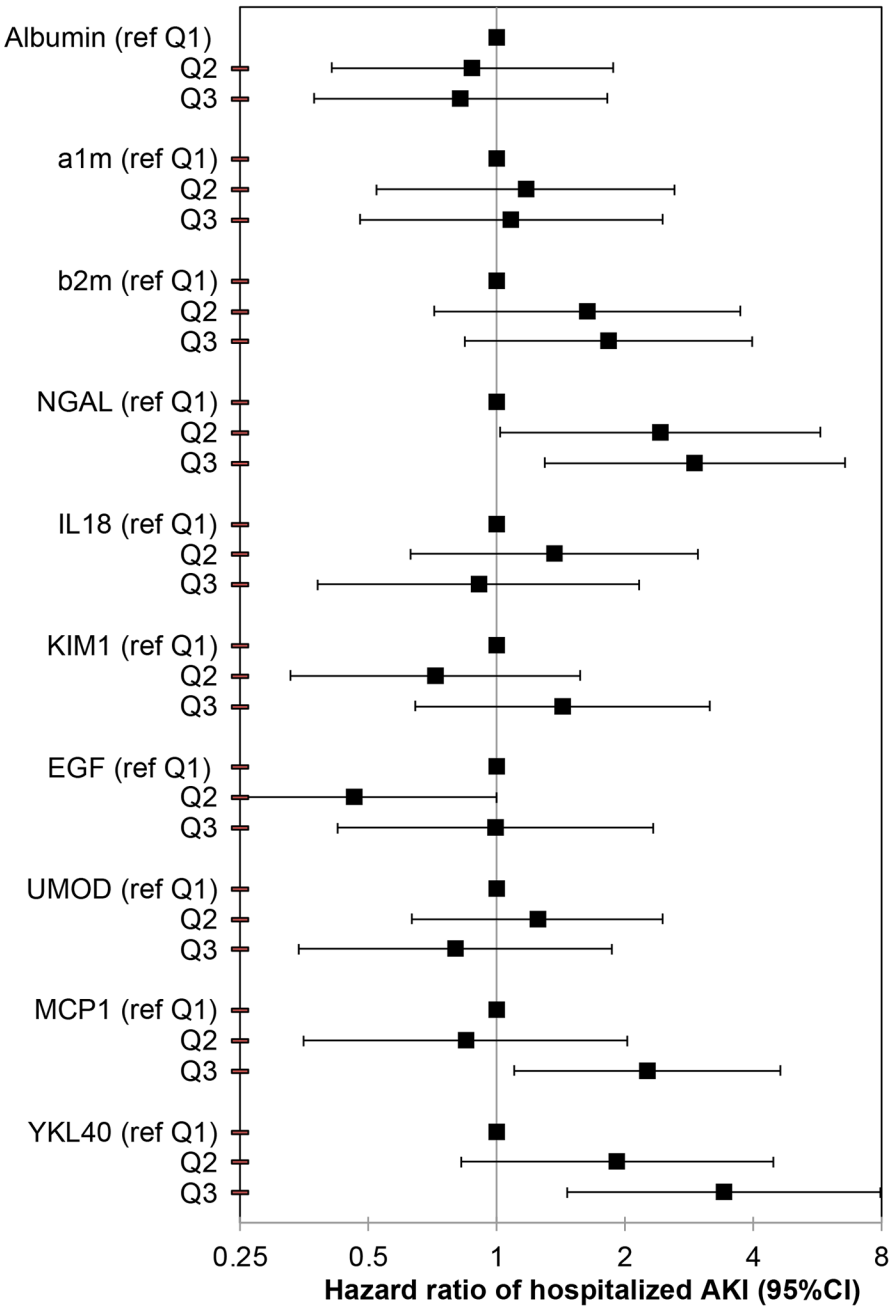

Figure 1:

Associations of kidney biomarkers with incident hospitalized AKI by Cox proportional hazards regression among people living with HIV.

Biomarkers are indexed to urine creatinine

Adjusted for sociodemographic factors (age, race/ethnicity, annual income, smoking history, injection drug history, education level), and comorbidities (diabetes, hypertension, hyperlipidemia, coronary artery disease, HCV, HIV disease course (history of AIDS, HIV medication exposures, CD4+ count and HIV viral load), CKD-EPI eGFR creatinine

Table 1:

Characteristics of PLWH enrolled in the PARIS Cohort, Overall and Stratified by Hospitalized AKI Status

Factor	No hospitalized AKI (N=406)	Hospitalized AKI (N=62)	Overall (N=468)
Age at enrollment, years	53 ± 9	52 ± 9	53 ± 9
Gender/Sex			
Male	224 (55)	31 (51)	255 (55)
Female	180 (45)	30 (49)	210 (45)
Race/ethnicity			
American Indian, Alaska Native	3 (0.7)	0 (0)	3 (0.6)
Asian	1 (0.2)	0 (0)	1 (0.2)
Black, African American	362 (90)	56 (92)	418 (90)
More than one race	11 (3)	0 (0)	11 (2)
White, Caucasian	27 (7)	5 (8)	32 (7)
Hispanic/Latinx	12 (3)	0 (0)	12 (3)
Annual Income			
less than $25,000	299 (88)	42 (93)	341 (89)
$25,000 - $49,999	29 (9)	3 (7)	32 (8)
$50,000 or more	12 (3)	0 (0)	12 (3)
Smoking			
never smoker	65 (16)	10 (16)	75 (16)
past smoker	83 (21)	15 (25)	98 (21)
current smoker	254 (63)	36 (59)	290 (63)
Injection Drug Use			
never injection drug use	243 (61)	35 (57)	278 (60)
past injection drug use	145 (36)	22 (36)	167 (36)
current injection drug use	13 (3)	4 (7)	17 (4)
Diabetes	53 (13)	16 (27)	69 (15)
Hypertension	176 (44)	42 (69)	218 (47)
Hyperlipidemia	123 (31)	18 (30)	141 (30)
Hepatitis C Infection	185 (46)	30 (50)	215 (47)
Estimated GFR (mL/min/1.73m^2)	75 ± 20	67 ± 23	74 ± 20
Albumin-creatinine ratio	78 (41, 255)	119 (51, 806)	81 (43, 268)
AIDS or AIDS-defining illness	175 (44)	31 (50)	206 (45)
CD4+ cell count (cells/mm^3)	538 (346, 798)	557 (225, 829)	540 (336, 799)
HIV viral load (copies/mL)	10 (10, 25)	10 (10, 49)	10 (10, 26)
Use of any NRTIs	170 (42)	20 (32)	190 (41)
Use of TDF	19 (5)	3 (5)	22 (5)
Use of any Non-NRTIs	65 (16)	15 (24)	80 (17)
Use of any Integrase Inhibitors	209 (52)	41 (66)	250 (54)

Factor	No hospitalized AKI (N=406)	Hospitalized AKI (N=62)	Overall (N=468)
Use of boosted Integrase Inhibitors	108 (27)	17 (27)	125 (27)
Use of boosted Protease Inhibitors	128 (32)	18 (29)	146 (31)

PARIS, Predictors of Acute Renal Injury Study; AIDS, acquired immune deficiency syndrome, NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate; ARV, anti-retroviral; GFR, glomerular filtration rate; HIV, human immunodeficiency virus

Data are presented as mean ± standard deviation for normally distributed variables, median (interquartile range) for skewed continuous variables, or n (%) for categorical variables.

Table 2.

Associations of urine biomarkers of kidney health with hospitalized AKI among PLWH

Baseline, per 2-fold higher	**Model 1*** **HR (95% CI)**	**Model 2**** **HR (95% CI)**
Glomerular/Endothelial Injury		
albumin	**1.14 (1.02, 1.27)**	0.95 (0.83, 1.09)
Tubular Dysfunction		
a1m	1.19 (0.98, 1.45)	1.03 (0.77, 1.37)
b2M	1.08 (0.98, 1.19)	1.04 (0.92, 1.18)
Tubular Injury		
NGAL	**1.22 (1.06, 1.40)**	**1.18 (1.01, 1.39)**
IL18	1.15 (0.91, 1.44)	1.02 (0.76, 1.37)
KIM-1	**1.40 (1.12, 1.74)**	1.25 (0.94, 1.67)
Tubular Synthetic Function and Resilience		
EGF	**0.65 (0.49, 0.85)**	0.75 (0.51, 1.10)
UMOD	**0.72 (0.56, 0.92)**	0.80 (0.60, 1.07)
Tubulointerstitial Inflammation and Fibrosis		
MCP-1	**1.30 (1.00, 1.69)**	1.15 (0.83, 1.58)
YKL40	1.12 (0.98, 1.27)	1.09 (0.94, 1.28)
Time-updated, per 2-fold higher	**Model 1*** **HR (95% CI)**	**Model 2**** **HR (95% CI)**
Glomerular/Endothelial Injury		
albumin	**1.14 (1.03, 1.27)**	1.03 (0.91, 1.16)
Tubular Dysfunction		
a1m	1.19 (0.98, 1.44)	1.05 (0.84, 1.32)
b2M	**1.12 (1.01, 1.23)**	1.05 (0.95, 1.17)
Tubular Injury		
NGAL	**1.24 (1.08, 1.42)**	**1.24 (1.06, 1.44)**
IL18	1.23 (0.99, 1.54)	1.15 (0.90, 1.48)
KIM-1	**1.45 (1.17, 1.80)**	**1.30 (1.02, 1.66)**
Tubular Synthetic Function and Resilience		
EGF	**0.66 (0.51, 0.86)**	0.92 (0.67, 1.25)
UMOD	0.86 (0.68, 1.09)	0.95 (0.73, 1.24)
Tubulointerstitial Inflammation and Fibrosis		
MCP-1	1.23 (0.94, 1.60)	1.11 (0.84, 1.46)
YKL40	**1.15 (1.01, 1.31)**	1.10 (0.97, 1.26)

HR (95% CI), hazard ratio and 95% confidence interval

*adjusted for urine Cr and sociodemographic factors (age, race/ethnicity, smoking history, injection drug history, education level)

**in addition to Model 1 covariates, adjusted for comorbidities (diabetes, hypertension, hyperlipidemia, coronary artery disease, HCV, HIV disease course (history of AIDS, HIV medication exposures, CD4+ count and HIV viral load), CKD-EPI eGFR, and albuminuria

UMOD and EGF: higher values are better; all other biomarkers: lower values are better

Table 3.

Associations of urine biomarkers of kidney health with all-cause hospitalization among PLWH

Baseline, per 2-fold higher	**Model 1*** **HR (95% CI)**	**Model 2**** **HR (95% CI)**
Glomerular/Endothelial Injury		
albumin	1.01 (0.93, 1.10)	0.95 (0.86, 1.05)
Tubular Dysfunction		
a1m	1.05 (0.92, 1.19)	1.05 (0.88, 1.25)
b2M	1.02 (0.95, 1.09)	1.03 (0.94, 1.11)
Tubular Injury		
NGAL	1.09 (0.98, 1.21)	1.04 (0.94, 1.16)
IL18	1.16 (0.98, 1.36)	1.09 (0.89, 1.33)
KIM-1	**1.18 (1.01, 1.38)**	1.12 (0.92, 1.35)
Tubular Synthetic Function and Resilience		
EGF	0.88 (0.72, 1.07)	0.88 (0.69, 1.12)
UMOD	**0.85 (0.72, 1.00)**	0.85 (0.71, 1.02)
Tubulointerstitial Inflammation and Fibrosis		
MCP-1	**1.22 (1.02, 1.47)**	**1.31 (1.08, 1.59)**
YKL40	**1.13 (1.04, 1.24)**	**1.11 (1.00, 1.24)**
Time-updated, per 2-fold higher	**Model 1*** **HR (95% CI)**	**Model 2**** **HR (95% CI)**
Glomerular/Endothelial Injury		
albumin	1.02 (0.94, 1.11)	0.98 (0.90, 1.07)
Tubular Dysfunction		
a1m	1.05 (0.93, 1.20)	1.06 (0.91, 1.23)
b2M	1.05 (0.98, 1.12)	1.04 (0.96, 1.12)
Tubular Injury		
NGAL	**1.14 (1.03, 1.27)**	**1.12 (1.01, 1.25)**
IL18	1.16 (0.99, 1.36)	1.14 (0.96, 1.35)
KIM-1	**1.23 (1.05, 1.43)**	**1.18 (1.00, 1.41)**
Tubular Synthetic Function and Resilience		
EGF	**0.83 (0.69, 1.00)**	0.85 (0.68, 1.06)
UMOD	0.85 (0.72, 1.01)	0.89 (0.75, 1.06)
Tubulointerstitial Inflammation and Fibrosis		
MCP-1	**1.22 (1.01, 1.46)**	**1.20 (1.00, 1.45)**
YKL40	**1.11 (1.01, 1.22)**	1.09 (0.99, 1.20)

HR (95% CI), hazard ratio and 95% confidence interval

*adjusted for urine Cr and sociodemographic factors (age, race/ethnicity, smoking history, injection drug history)

**in addition to Model 1 covariates, adjusted for comorbidities (diabetes, hypertension, hyperlipidemia, coronary artery disease, HCV, HIV disease course (history of AIDS, HIV medication exposures, CD4+ count and HIV viral load), CKD-EPI eGFR, and albuminuria

UMOD and EGF: higher values are better; all other biomarkers: lower values are better