POSTER #730

Validation of a Chronic Kidney Disease Risk Score in HIV+ Patients in the U.S.

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BACKGROUND

- The risk of chronic kidney disease (CKD) increases with both HIV infection and aging, substantially complicating clinical decision-making
- The ability of clinicians to assess CKD risk prior to prescribing antiretroviral (ARV) therapies is constrained by the lack of a widely applicable, easy to calculate, risk assessment tool
- The Data collection on Adverse events of Anti-HIV Drugs (D:A:D) developed and self-validated a CKD risk score in HIV+ patients using data primarily from European and Australian clinical practices and two international clinical trials[1]
- There is a great geographic variability in HIV+ patient characteristics, clinical practice and estimated glomerular filtration rate (eGFR) measurement
- Validation of the D:A:D CKD risk score will facilitate identification of HIV+ patients at greatest risk for moderate to severe CKD, information which is a key part of clinical decision-making

OBJECTIVE:

To assess the validity of the D:A:D risk score model for CKD in an exclusively U.S. based cohort of HIV+ patients.

METHODS

Data Source

Observational Pharmaco-Epidemiology Research & Analysis (OPERA) database

- Electronic health records following 78,698 HIV+ patients
- 79 US community-based outpatient clinics in 15 states

Study Population

- HIV+ adults in the OPERA database with:
  - ≥ 1 HIV-1 viral load test and CD4 lymphocyte test in the 12 months on or prior to the date of the first observed eGFR >60 ml/min/1.73 m^2 test result (index)
  - No previous exposure to potentially nephrotoxic antiretroviral agents (tenofovir disoproxil fumarate, atazanavir, boosted atazanavir, boosted lopinavir, or other boosted protease inhibitors)
  - No history of kidney transplant, dialysis or moderate/severe CKD diagnosis (≥ Stage 3)
  - ≥ 3 eGFR measurements on or after baseline
  - ≥ 1 eGFR test result >60 ml/min/1.73 m^2 during observation period
- Baseline: First observed eGFR >60 ml/min/1.73 m^2 between 1/1/2002 and 12/31/2016
- Censoring: Last eGFR test result, occurrence of the study outcome, lost to follow-up, or study end (07/31/2017)
- 3 validation cohorts were drawn independently using varying methods for calculating eGFR: MDRD, Cockcroft- Gault and CKD-EPI eGFR estimates (Table 1)

CKD Measurement

- GFR is generally estimated (eGFR) from serum creatinine in combination with other factors (Table 1)

Outcome

Development of moderate to severe CKD defined as ≥2 consecutive eGFR test results <60 ml/min/1.73 m^2, >90 days apart

D:A:D CKD Risk Score

- Full and short risk scores calculated by adding coefficients associated with baseline risk factors (Figure 1)
- Coefficients from the D:A:D risk score were directly applied to eligible OPERA patients, but the risk score itself was not recreated and/or recalibrated
- Patients were categorized based on their risk of moderate to severe CKD as:
  - Low risk: score <0
  - Medium risk: score 0-4
  - High risk: score ≥5

Statistical Analysis

- The 12-month baseline period preceding the index date was used to assess patient demographics and clinical characteristics
- We replicated the same five metrics employed by D:A:D in their self-validation study[1]
  1. Observed crude incidence rates within risk score strata
  2. Kaplan Meier probability of progression
  3. Unadjusted incidence rate ratios (IRR)
  4. Adjusted IRR (aIRR) from Poisson model associated with a one-point increase in the risk score on CKD incidence
  5. Model discrimination (Harrell's c-statistic)
- Since differences in population characteristic can result in a differential incidence of CKD, we focused on incidence-independent metrics (IRR, aIRR, model discrimination) to assess the validity of the risk score

Table 1. eGFR Calculation

Modification of Diet in Renal Disease (MDRD) $eGFR = 186.3 \times serum\ creatinine^{-1.154} \times Age^{-0.203} \times [0.742\ if\ Female] \times [1.212\ if\ African\ American]$	
+ Most frequent method used by laboratories in the United States to report eGFR	- Developed among persons with eGFR ≤90 mL/min/1.73 m^2 - Not validated among persons with normal kidney function - May underestimate higher GFR and thus overestimate CKD incidence (particularly for early stages) - Accuracy may vary based on race
Cockcroft-Gault (C-G) $Creatinine\ Clearance = \frac{(140 - Age) \times Weight\ in\ kg \times [0.85\ if\ Female]}{72 \times serum\ creatinine}$	
+ Used to develop the D:A:D risk score	- Estimates creatinine clearance instead of eGFR (overestimates eGFR) - Not adjusted for body surface area or race
Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), 2009 $eGFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times [1.018\ if\ Female] \times [1.159\ if\ Black]$ where SCr =serum creatinine in mg/dL, κ = 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr /κ or 1, and max indicates the maximum of SCr/κ or 1	
+ Validated in several populations + Recommended by the 2016 European AIDS Clinical Society (EACS) Guidelines and the Kidney Disease, Improving Global Outcomes (KDIGO) + Reduced bias at eGFR >60 mL/min/1.73 m^2	- A newer formula incorporating serum cystatin C instead of serum creatinine has been developed and is more accurate

RESULTS

Figure 1. Baseline Patient Characteristics and D:A:D Full and Short Risk Score Calculation, by OPERA Validation Cohort

Darker shaded bars represent characteristics included in the D:A:D risk score.
Lighter shaded bars represent characteristics not included in the D:A:D risk score.

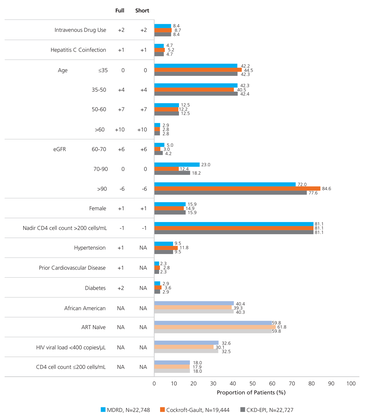


Table 2. Comparison of CKD Risk Score: Distribution & Discrimination, by Study Population

	OPERA (MDRD)	OPERA (C-G)	OPERA (CKD-EPI)	D:A:D Derivation (C-G)	D:A:D Self-Validation (CKD-EPI)
N	22748	19444	22727	17954	2013
Full Score					
All Patients, Median (IQR)	-3 (-6 to 3)	-3 (-7 to 0)	-3 (-7 to 1)	-2 (-4 to 2)	-2 (-3 to 1)
Patients who devloped CKD, Median (IQR)	6 (3 to 10)	7 (2 to 12)	6 (1 to 10)	10 (5 to 14)	9 (0 to 12)
Harrell's C-Statistic	0.87	0.92	0.88	0.92	0.87
Short Score					
All Patients, Median (IQR)	-3 (-7 to 2)	-3 (-7 to -1)	-3 (-7 to 0)	-2 (-4 to 2)	NA
Patients who devloped CKD, Median (IQR)	5 (3 to 10)	6 (1 to 12)	6 (1 to 10)	10 (5 - 13)	NA
Harrell's C-Statistic	0.87	0.91	0.88	0.91	NA

- Results for the validation of the full and short risk scores followed similar patterns
- CKD incidence [Figure 2], CKD probability [Figure 3] and incidence rate ratio [Figures 4 and 5] results are presented for the full risk score validation only

Figure 2. Crude CKD Incidence* and 95% Confidence Intervals, by Study Population and CKD Risk Group (Full Risk Score)

**Crude CKD Incidence represents the number of CKD cases observed for every 1,000 person-years of follow-up*

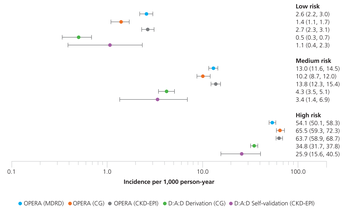


Figure 3. Probability of Progression to CKD and 95% Confidence Intervals Estimated from Kaplan Meier Curves, by Study Population and CKD Risk Group (Full Risk Score)

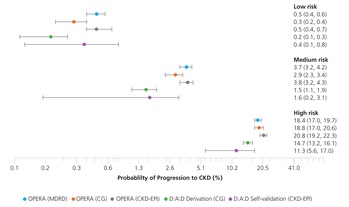


Figure 4. Incidence Rate Ratios and 95% Confidence Intervals for the Association Between CKD Development and CKD Risk Group, with Medium Risk as the Referent (Full Risk Score)

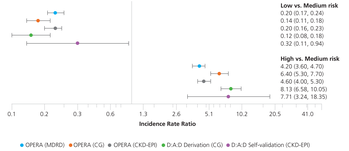
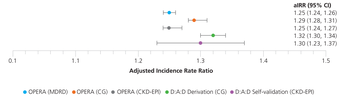


Figure 5. Adjusted* Incidence Rate Ratio and 95% Confidence Intervals for the Association Between CKD Development and a One-Point Increase in the Continuous CKD Risk Score (Full Risk Score)

** Modeling in the D:A:D derivation cohort was adjusted for baseline intravenous drug use, gender, hepatitis C coinfection, age, nadir CD4 count, eGFR, hypertension, prior CVD and diabetes. Models in all other cohorts were not further adjusted.*



DISCUSSION

- Patient demographics and clinical characteristics were similar across all 3 OPERA validation cohorts (Fig.1) but differed notably from the D:A:D derivation cohort - differences may reflect temporal, regional or healthcare system specific variation in both HIV population and/or treatment patterns
- CKD incidence varied by eGFR formula but increased according to risk strata in all 3 OPERA cohorts (Fig. 2). CKD incidence was slightly higher in all 3 OPERA cohorts than in the D:A:D derivation cohort
- Compared to the medium full risk group, being in the low risk group appeared protective (OPERA IRR for CKD ranging from 0.14 to 0.20 vs. D:A:D derivation IRR of 0.12, all with overlapping confidence intervals) and being in the high risk group appeared harmful (OPERA IRR ranging from 4.2 to 6.4 vs. D:A:D IRR of 8.1), with overlapping confidence intervals in OPERA C-G (Fig. 4)
- Harrell's c-statistic in OPERA full risk models ranged from 0.87-0.92 vs. D:A:D c-statistic of 0.92 (Table 2) suggesting that the ability to discriminate between low, medium and high risk groups was similar in both validation studies
- aIRR in OPERA full risk models ranged from 1.25 to 1.29, similar to the D:A:D aIRR of 1.32, with overlapping confidence intervals in the OPERA C-G (Fig. 5)
- Similar patterns were observed using the short risk score (data not shown). The OPERA short risk score aIRR (range: 1.25-1.30) closely approximated the D:A:D short risk score aIRR (1.33), with all confidence intervals overlapping
- Sample sizes in the OPERA validation cohorts were ~10 times larger than the D:A:D self-validation cohorts, resulting in notably narrower confidence intervals
- IRR, aIRR, and c-statistics all support validation of the D:A:D CKD risk score in all three OPERA validation cohorts regardless of eGFR equation

KEY FINDING:

This study supports the validity of the D:A:D short and full risk scoring methods for assessing the probability of CKD in HIV+ patients in the United States, regardless of the eGFR equation employed. The ability to identify HIV+ patients at greatest risk for moderate to severe CKD is an essential component of clinical decision-making.

REFERENCE

1. Mocroft, A., et al., Development and validation of a risk score for chronic kidney disease in HIV infection using prospective cohort data from the D:A:D study. PLoS Med, 2015. 12(3): p. e1001809.

ACKNOWLEDGMENTS

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