Comparison of CKD-EPI and MDRD to estimate baseline renal function in HIV-positive patients

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Abstract

Background. Renal dysfunction is common in HIV-positive patients, and guidelines suggest regular monitoring of renal function with estimated glomerular filtration rate (eGFR) and urinalysis. It is unknown whether Chronic Kidney Disease Epidemiological Collaboration (CKD-EPI) or Modification of Diet in Renal Disease (MDRD) provide better estimates of glomerular filtration rate (GFR) in this population.

Methods. We compared the CKD-EPI and MDRD equations to estimate GFR at baseline in 20,132 HIV-positive individuals in the UK CHIC cohort. Kappa statistics and Bland–Altman plots were used to assess agreement between the two estimates and Kaplan–Meier plots and Cox regression analysis to describe mortality patterns.

Results. At baseline, median eGFR was 100 (87, 112) (CKD-EPI) and 94 (83, 108) (MDRD) (mL/min/1.73m²). Good overall agreement between CKD-EPI- and MDRD-defined eGFR bands was observed (Kappa = 0.71, 95% confidence interval: 0.70–0.72). Of the 367 patients with eGFR MDRD 30–59, 57 (15.5%) were categorized as eGFR 60–89 by CKD-EPI. After adjustment for covariates, eGFR <60 (CKD-EPI), eGFR <30 (MDRD) and eGFR /C211 were significantly associated with an increased risk of death. Mortality in patients classified as having eGFR 60–89 by CKD-EPI and eGFR 30–59 by MDRD more closely resembled mortality of patients who had eGFR 60–89 by both formulae.

Conclusions. MDRD and CKD-EPI equations showed a high degree of agreement in stratifying patients by baseline eGFR. CKD-EPI estimates of GFR <60 at baseline are more strongly associated with mortality than MDRD estimates of GFR <60, supporting the concept that MDRD may have overestimated the severity of renal impairment in these patients. Our findings support the use of CKD-EPI in HIV-positive individuals.

Keywords: chronic kidney disease; CKD-EPI; eGFR; HIV; MDRD

Introduction

Chronic kidney disease (CKD) is an important cause of morbidity and mortality in HIV-positive individuals [1]. Impaired renal function, defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m² at baseline and prior to commencing combination antiretroviral therapy (cART), is an independent predictor of death [2–4]. Guidelines for the management of CKD in HIV-positive patients highlight the importance of early recognition of impaired renal function to prevent progression and limit complications [5]. While Cockcroft–Gault [6] and the four-variable Modification of Diet in Renal Disease (MDRD) [7] are most often used to calculate eGFR, the recently developed Chronic Kidney Disease Epidemiological Collaboration (CKD-EPI) [8] formula may provide a more reliable estimate of eGFR for those with relatively well preserved renal function [9].

The MDRD formula was derived in American patients with underlying kidney disease [7]. It has not been validated for use in other patient populations and is inaccurate at eGFR levels >60 mL/min/1.73m² [7]. Despite this, MDRD has been widely used as an epidemiologic tool to estimate associations of CKD with survival in general population studies [10]. However, when used in general populations, MDRD tends to overestimate the degree of renal impairment, particularly in women [11–13]. This led to the establishment of an international collaborative group which pooled all data-sets with gold standard measures of glomerular filtration rate (GFR) and derived the CKD-EPI formula for use with isotope dilution mass spectrometry (IDMS) calibrated creatinine measurements [8].

CKD-EPI and MDRD have not been validated for estimating GFR in HIV-positive patients [14]. Nonetheless, with mild–moderate renal impairment being relatively common [15–17], there is a strong incentive to use...
GFR-estimating formulae in HIV-positive patients. Hence, we assessed the overall agreement between eGFR estimates obtained with the CKD-EPI and MDRD formulae and investigated the effect of baseline eGFR on mortality, in particular in those who were re-categorized by CKD-EPI from Stage 3 CKD to Stage 2 eGFR.

Materials and methods

Data were obtained from the UK Collaborative HIV Cohort (CHIC) study [18], an observational cohort study of HIV-positive individuals aged ≥16 years who have attended some of the largest HIV clinics in the UK as of January 2016. The present analyses include data up to December 2008 and were restricted to seven centres that routinely contributed serum creatinine data. Information from the Office of National Statistics death register is used to ensure optimal ascertainment of deaths among patients who are lost to follow-up. The study was approved by the NHS Research Ethics Committee.

All available serum creatinine values were converted into eGFR, using age, gender, ethnicity and the CKD-EPI and MDRD equations. As acute renal failure is particularly common within 3 months of HIV diagnosis [19] and CKD is defined by the presence of abnormal renal function for >3 months, baseline renal function was based on the first available serum creatinine measurement obtained >3 months from cohort entry. eGFR was stratified into bands based on CKD staging [Stage 1: ≥90; Stage 2: 60–89; Stage 3: 30–59; Stage 4: 15–29 and Stage 5: <15 (mL/min/1.73m²)] [20]. For simplicity, we have omitted the eGFR units (mL/min/1.73m²) in the remainder of the manuscript.

Statistical analysis

Data were analysed using STATA (version 11, Stata Corporation; College Station, TX; Austin, TX). The kappa statistic was used to assess the agreement between CKD-EPI- and MDRD-derived eGFR values. The standard deviation (SD) of the difference between the estimates from the two formulae [21] were used to show the bias between CKD-EPI- and MDRD-derived eGFR values. The kappa statistic was used to assess the agreement between the two formulae, taking the difference between the two values to be used to estimate the limits of agreement.

Follow-up time was calculated from baseline to the date of death or censoring (last clinic visit or 31 December 2008, whichever occurred first). Cox proportional hazards regression modelling was used to assess the effect of baseline eGFR, as defined by the two formulae, on mortality. Associations between baseline eGFR and death were adjusted for the following fixed covariates: demographics (age, gender, ethnicity, HIV exposure group and year of entry into cohort), prior AIDS diagnosis, CD4 cell count and HIV RNA at baseline, hepatitis B surface antigen (HBSAg) and hepatitis C antibody (HCV) status and exposure to cART (yes/no), with the value of each covariate taken as the value closest to the time of baseline eGFR measurement. All statistical tests are two sided and associations with P-values ≤0.05 were considered statistically significant. As previous analyses from the study have demonstrated that ethnicity may modify the prognostic value of eGFR [22], sensitivity analyses were performed whereby associations with mortality were assessed separately in those of black and non-black ethnicity. Kaplan–Meier graphs were used to assess mortality in patients with Stage 2 eGFR and Stage 3 eGFR with both CKD-EPI and MDRD and in those who had Stage 2 eGFR with CKD-EPI and Stage 3 eGFR with MDRD.

Results

Of the 27 577 patients who received care during the study period, 5119 (19%) had no renal function data, 2326 (8%) had died or became lost to follow-up within 3 months of cohort entry; the remaining 20 132 (73%) were included in analyses. Patients without renal function data had similar CD4 cell counts at baseline but were more likely to be male, to have sex between men or intravenous drug use (IVDU) as risk factor for HIV acquisition and a lower prevalence of viral hepatitis (B and C) co-infection compared to those included in the analyses (data not shown). Of those included into the analyses, 78% of patients were male, 25% of black ethnicity, 5.3% HBSAg positive and 7.7% HCV antibody positive. At baseline, the median [inter-quartile range (25th and 75th percentiles)] age was 34 (30, 40) years, the median CD4 cell count 350 (208, 520) cells/mm³ and 80% of patients had commenced cART (Table 1).

The baseline eGFR was assessed at a median of 4 (3, 13) months from cohort entry, which was a median of 5 (3, 13) months from HIV diagnosis. The median eGFR was 100 (87, 112) by CKD-EPI and 94 (83, 108) by MDRD. Good overall agreement was observed between CKD-EPI- and MDRD-derived eGFR bands [kappa = 0.71, 95% confidence interval (CI): 0.70–0.72], with the best agreement observed for those with eGFR <30 or ≥90 (Table 2). CKD (eGFR < 60) was present at baseline in 2.0% (CKD-EPI) and 2.3% (MDRD), respectively; 57 (15.5%) patients with Stage 3 eGFR measurements by MDRD had Stage 2 measurements by CKD-EPI (Stage 3 discordant eGFR). Figure 1 shows the Bland–Altman plot of agreement between MDRD and CKD-EPI equations. Overall, the mean (SD) difference between the estimates from the two formulae was −2.82 (8.49) with limits of agreement of −19.46 to 13.81, with good agreement observed between the two formulae when the average eGFR value was ≤120 [mean difference −4.37 (3.48), limits of agreement −11.19 to 2.44] (Figure 1B).

In the absence of gold standard GFR, we used mortality analyses to evaluate which eGFR formula may more closely reflect renal function. Both formulae derive from serum creatinine, where high serum creatinine may be a result of high muscle mass (which is beneficial for survival) or decreased GFR (which is a poor prognostic factor) and vice versa for low serum creatinine levels. Thus, mortality associations for those who show disagreement by eGFR formula are indirectly informative on whether the disagreement may be driven by one of the two formulae better estimating renal function or not. Patients were followed for a median of 5.3 (2.0, 8.9) years during which 1820 patients (9%) died [overall mortality rate 1.60 (95% CI 1.53–1.68) per 100 person-years]. The median baseline eGFR was lower [98 versus 100, P < 0.001 (CKD-EPI) and 93 versus 95, P = 0.0002 (MDRD)] for patients who died compared to those who survived. In unadjusted models, the cumulative hazard of all-cause mortality was increased in patients with CKD at baseline. After adjustment for covariates, eGFR <30 and 30–59, as defined by CKD-EPI, remained significantly associated with an increased risk of death. By contrast, only eGFR <30 was significantly associated with death when MDRD was used to calculate eGFR (Table 3). Patients with eGFR 60–89 at baseline were at lowest risk of death, regardless of the estimation algorithm. Although the association between baseline eGFR and mortality was affected by ethnicity (P < 0.001 for interaction), similar hazard ratios (HRs) estimates were obtained for patients of black and white/other ethnicity with CKD-EPI and MDRD (Supplementary Table). In addition to those with reduced eGFR, patients with baseline eGFR ≥105 were at increased risk of death. Compared to patients with eGFR 90–104, those with eGFR ≥105 were younger, more often female and of black ethnicity, with no difference in HIV parameters or hepatitis co-infection status (Table 3).

Cumulative mortality in patients with eGFR 60–89 and 30–59 (as calculated with both CKD-EPI and MDRD), and
in those who were re-categorized from eGFR 30–59 with MDRD to 60–89 with CKD-EPI, is shown in Figure 2. After adjustment for age, ethnicity, risk group, AIDS, years since cohort entry and CD4 cell count, HIV RNA level, cART use, HBsAg and HCV status at baseline, mortality in re-categorized patients was somewhat lower than mortality in patients with eGFR 30–59 by both formulae [adjusted hazard ratio (aHR) 0.60 (0.23, 1.61)] and somewhat higher than mortality in patients with eGFR 60–89 by both formulae [aHR 1.16 (0.46, 2.99)].

Discussion

In this large sample of HIV-positive individuals in the UK, we observed a good correlation between CKD-EPI and MDRD at eGFR ≤120. In this range, the CKD-EPI formula on average gave somewhat higher eGFR estimates than the MDRD formula, resulting in smaller numbers of patients with CKD (eGFR < 60) at baseline and stronger associations between CKD at baseline and subsequent mortality. Our data are consistent with observations in the general population that suggest that MDRD may overestimate the severity of renal impairment.

Studies in the general population comparing CKD-EPI and MDRD against isotopic GFR observed less bias, improved precision and greater accuracy with CKD-EPI [8], although others have found lesser mean bias with MDRD [23]. Consistent with Levey et al. [8], we observed somewhat lower mean eGFR values with MDRD compared to CKD-EPI in subjects with eGFR ≤120. By contrast, in those with eGFR > 120, CKD-EPI gave lower mean eGFR estimates than MDRD. In this range, however, neither MDRD nor CKD-EPI have been validated and without gold standard validation data, it is unclear in our study whether CKD-EPI > 120 identifies a population with abnormally low serum creatinine values, glomerular hyperfiltration or reflects the inadequacy of both formulae to accurately predict eGFR in this subset of patients. When the use of CKD-EPI in our cohort was restricted to patients with an average eGFR ≤120, the mean difference between the two eGFR estimates was −4.4 mL/min/1.73m² with narrow limits of agreement. Of note, the bias of MDRD and CKD-EPI (relative to measured GFR) may be affected by gender, age and GFR [23]; as these parameters tend to differ between HIV cohorts, our results should be interpreted with a degree of caution and confirmed in other HIV populations.

Few studies have evaluated GFR prediction equations in HIV-positive individuals, and most do not include CKD-EPI [24–26]. One study of 106 HIV-positive patients observed good correlation between CKD-EPI and cystatin C (r = −0.671, P < 0.001), with cystatin C correlating well with measured GFR (r = −0.760, P = 0.001) [27]. However, correlation is not necessarily the optimal method of evaluation as this merely measures the strength of a relationship between two variables, not the agreement between them [21].

We also used the two formulae to estimate eGFR at baseline and used these estimates as predictor of all-cause mortality.
mortality. Patients with CKD were at increased risk of death. Consistent with the more restrictive definition of CKD, the association between CKD and death was somewhat stronger when CKD-EPI was used to estimate renal function. A significantly increased risk of death was observed for patients with eGFR >90 and eGFR 30–59 (relative to those with eGFR ≥90) when calculated by CKD-EPI, while statistical significance was only observed for patients with eGFR <30 when calculated by MDRD. The patients reclassified by CKD-EPI as not having CKD had similar survival to those who were consistently categorized by both formulae as Stage 2, suggesting that CKD-EPI correctly identifies and re-classifies those at low risk of adverse outcomes. This has also been demonstrated in the general population. In the Atherosclerosis Risk in Communities (ARIC) study, CKD-EPI reclassified 44.9 and 43.9% of those with eGFR 60–89 and eGFR 30–59, respectively, to a higher eGFR category [28]. Patients that had been reclassified upwards had lower risk for renal disease progression, all-cause mortality, coronary heart disease and stroke compared to those who had not been reclassified [28]. An Australian study showed similar all-cause mortality in patients reclassified as having no CKD and patients without CKD [29]. The results of these studies are in agreement with our observations and suggest that CKD-EPI may be more useful to estimate baseline eGFR as predictor of subsequent mortality in general and HIV-positive populations.

The strengths of this study include the large sample size and prolonged follow-up. Limitations include the small numbers of patients with CKD or who were re-categorized from Stage 3 to Stage 2 with CKD-EPI, the lack of data on diabetes, hypertension and proteinuria, which prevents us from identifying patients with CKD Stages 1 and 2, lack of data on weight, anti-hypertensives, causes of death and the lack of gold standard GFR measurements in the absence of which we are unable to directly validate CKD-EPI or assess the accuracy of the two equations. Finally, we have not accounted for small differences in creatinine calibration between contributing laboratories and black patients and
those with viral hepatitis were slightly over-represented in our analyses.

The ideal biomarker for estimating GFR in HIV-positive patients remains to be defined [14]. Serum creatinine is inexpensive, widely available and, when converted into eGFR, a highly useful epidemiological tool. In agreement with observations in the general population, our data support the use of CKD-EPI to calculate eGFR in HIV-positive patients.

**Supplementary data**

Supplementary data are available online at http://ndt.oxfordjournals.org.

**Acknowledgements.** F.I., C.S. and F.A.P. designed the study. F.I. performed the analyses with input from R.J., D.N., C.S. and F.A.P. F.I. and L.H. wrote the manuscript with input from all authors. The final version of the manuscript was approved by all authors. The authors wish to acknowledge the contribution of all members of UK CHIC and the UK CHIC/CKD study group (see Appendix).

**Sources of Funding.** This work was funded by the Medical Research Council, UK (Grants G00001999 and G0600337 to C.S.). The views expressed in this manuscript are those of the researchers and not necessarily those of the MRC. L.H. was funded by the National Institute for Health Research, UK. Part of this paper was presented at the 12th International Workshop on Adverse Drug Reactions and Co-morbidities in HIV, 4–6 November 2010, London, UK.

**Conflict of interest statement.** None of the authors has any financial or personal relationships with people or organizations that could inappropriately influence this work, although many members of the group have, at some stage in the past, received funding from a variety of pharmaceutical companies for research, travel grants, speaking engagements or consultancy fees.

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Received for publication: 2.8.11; Accepted in revised form: 12.10.11

Appendix

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