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CLINICAL PREDICTION TOOLS FOR KIDNEY DYSFUNCTION: THEIR APPLICATION TO HIV PATIENTS IN A TERTIARY CARE CENTRE IN SOUTH EAST NIGERIA

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***Abstract*: The World Health Organization (WHO) recommends the use of tenofovir as part of first line regimen for the management of Human Immunodeficiency Virus (HIV). Tenofovir can be nephrotoxic necessitating renal function assessment before its commencement. This may be a challenge in resource poor settings. Clinical Prediction Tools (CPT) for kidney dysfunction have been developed and can help to determine patients who will not require creatinine testing. For this study, data were obtained from HIV patients and analysed using three CPTs. Using a cut-off of ≥ 2 for Primary CPT and BMI CPT, 3.3% of the patients will not require creatinine testing before treatment, and for Alternate CPT, 26.4% of the patients will not require creatinine tests. The preferred CPT for our patients is the Alternate CPT because the proportion of patients who will not require creatinine testing is comparable with its prediction.**

***Keywords*: Clinical Prediction Tool, creatinine, kidney dysfunction, HAART, HIV, Tenofovir.**

I. INTRODUCTION

In 2009, the World Health Organization (WHO) recommended that antiretroviral treatment (ART) programmes begin using tenofovir-based or zidovudine-based first line ART. These recommendations were made to avoid the unpleasant, disfiguring and sometimes life-threatening toxicity of stavudine, the need to select regimens suitable for use in many of patient groups, and maximize the benefits of using fixed dose combination.(1) A study carried out in Lesotho showed that patients whose medication included zidovudine were twice or more likely to have a toxicity-driven regimen substitution when compared with tenofovir. This risk of a toxic regimen switch was nearly 6 times as high for patients on stavudine than tenofovir. Their results agree with the latest WHO guidelines for the use of tenofovir as first line regimen, seeing that it is more tolerable and has a once-daily dosing.(2)

Systematic reviews and metanalyses have shown that tenofovir can be nephrotoxic, and also chronic kidney disease has also been found to be prevalent in HIV infected individuals.(3) WHO recommends that tenofovir should be dose reduced or avoided in case of decreased kidney function with estimated creatinine clearance of 50 mL/min, based on the Cockroft–Gault (CG) formula.(1)

Creatinine is a breakdown product of creatine phosphate from muscle and metabolism of protein. It is excreted at a constant rate by the body.(4) Serum creatinine measurement is a key indicator of kidney health because it is a by-product of muscle metabolism that is excreted unchanged by the kidneys and can easily be measured. Its value also depends on muscle mass. Creatinine is produced through a biological system involving creatine, phosphocreatine (also named creatine phosphate), and adenosine triphosphate (ATP, the body's instant and ready energy supply).(5) Creatinine is filtered from the blood through the kidneys, primarily by glomerular filtration, next by proximal tubular secretion. If this filtration process by the kidney is deficient, the level of blood creatinine rises. Every day, about 1% to 2% of muscle creatine is changed to creatinine. Men tend to have a more concentrations of creatinine than women do as a result of the fact that they have a higher skeletal muscle mass. Increased intake of creatine as can occur with eating lots of protein (like meat) can also increase daily creatinine excretion.(6-8)

Levels of blood creatinine vary and are determined by a number of factors such as gender, age, race, and body mass. Normal creatinine level in serum ranges from 0.6–1.1 mg/dL in adolescents aged 16 and above and women, 0.8–1.3 mg/dL in adolescents aged 16 and above and men, 0.2 or more in infants, and depends on muscle development. Serum creatinine levels and range are lower for women due to lower muscle mass and therefore, a lower rate formation and excretion of creatinine. Normal range of blood creatinine levels also differ by race. The mean blood creatinine is 1.25 mg/dL for men and 1.01 mg/dL for women for non-Hispanic blacks. On the other hand, in non-Hispanic whites, the average blood creatinine levels are 1.16 mg/dL for men and 0.97 mg/dL for women, and in Mexican-Americans the values are 1.07 mg/dL for men and 0.86 mg/dL for women.(9)

High levels of creatinine could indicate dehydration or kidney damage. A creatinine level is considered high for levels over 1.3 depending on factors such as race, age, gender, and body size. A number of conditions may cause a person to have higher than normal levels of creatinine. People who have only one kidney could have normal creatinine level of about 1.8 or 1.9. Levels of creatinine greater or equal to 2.0 in infants and greater than 5.0 in adults often points to severe kidney damage. People who are dehydrated could have elevated creatinine levels. Lower creatinine levels usually occur in patients who have low muscle mass and are not usually considered a serious medical problem.(9)

Clinical prediction tools (CPTs) are research-based tools that quantify the contributions of relevant patient characteristics to provide numeric indices that assist clinicians in making predictions. Clinical prediction tools are used to describe the possibility of the presence or absence of a certain condition, assisting in predicting patient prognosis, and helping with classification of patients for treatment.(10) Clinical prediction tools/rules/models are developed by applying statistical techniques to find combinations of predictors that categorize a heterogeneous group of patients into subgroups of risk. Over the years, there has been an increase in the development and validation of clinical prediction tools.

It is also important to evaluate the validity and reliability of these prediction tools before application. Development of valid and correct clinical prediction tools are done by following up a group of patients which is representative of the rest, by evaluating all factors that can be potential predictors and testing their independent contributions of each predictor variable, and by ensuring that the outcomes were independent of the predictors. To evaluate the results of any article that describe a clinical prediction tool, clinicians need to know what the prediction tool is, how well it classified patients into different levels of risk, and what the confidence intervals are around the risk estimates. Valid prediction tools are not applicable in every patient population. Before application to patients' management, the clinician should make sure that the tool maintains its prediction power in a new sample of patients, that the patients are similar to patients used to test the tool, and there is evidence that the tool has shown better judgement in clinical decision-making.(11)

Cross-sectional data collected routinely from HIV-positive patients attending the Sihanouk Hospital Center of HOPE, Phnom Penh, were used to generated a clinical prediction tool (CPT) for targeted creatinine testing during pre-antiretroviral therapy (ART) evaluation. The tool can be used to prevent unnecessary renal function assessment before the initiation of the nephrotoxic antiretroviral, tenofovir. This has become increasingly important given the World Health Organisation's (WHO's) recommendation of tenofovir in first-line ART(13-14) and expanding global use of tenofovir.(14-16)

The 2013 revised WHO guideline recommends targeted testing for creatinine before commencement of tenofovir. In contrast with testing for creatinine routinely, targeting individuals who have a higher probability of kidney dysfunction for testing can help to save scarce resources, particularly in resource-poor settings, while still able to identify those with high risk of kidney dysfunction. Despite the risk factors for kidney disease in the 2013 WHO guidelines, practical application on how to use them for targeted testing is lacking. However, these approaches should be clear, evidence based, easy to do in the clinic setting. A number of clinical prediction tools (CPTs) have been developed and their use is becoming widespread. CPTs are tools with which clinicians make decision, often relying on basic readily available clinical information.(17)

The primary outcome was kidney dysfunction (KD) at pre-ART evaluation, defined as an estimated creatinine clearance <50mL/min based on the Cockroft-Gault equation. The WHO recommends avoiding tenofovir or reducing its dose at this level of renal impairment.(75,76) A risk prediction score that included age, body weight and haemoglobin, being referred to as the primary CPT, achieved an Area Under the Receiver Operating Characteristic (AUROC) curve of 0.81 (95%CI 0.76 to 0.86) in their validation dataset. The probability of kidney disease ranged from 1.0% in those with a score of 0 to 51.2% in those with a score of 5. Using a cut-off score set at ≥2, sensitivity was 91.5%, specificity was 54.7%, and creatinine testing would have been avoided in 50.5% of patients. When body weight is replaced with BMI, referred to as the BMI CPT, achieved an AUROC of 0.77 (95%CI 0.72 to 0.83) however sensitivities and specificities were not described. With an alternative risk prediction score which has a 4-item score including age, body weight, sex, and WHO stage, hereafter referred to as the alternate CPT, AUROC was 0.81 (95%CI 0.76 to 0.85). Using a cut-off score of ≥2, sensitivity was found to be 95.8%, specificity was 40.7%, therefore creatinine testing could have been avoided in 37.4% of patients.(18)

In resource poor settings, there may be delay in getting laboratory results due to financial, logistics and manpower challenges. This will pose a problem for the implementation of 'Test and Treat' strategy.(19) The adoption of a CPT for creatinine will improve service delivery. This study aimed at applying our patients' data to the different CPTs and adopting one CPT for our use.

II. RESEARCH METHODS

The study area was the Anti-Retroviral Therapy (ART) clinic of Chukwuemeka Odumegwu Ojukwu University Teaching Hospital (COOUTH), Awka, Anambra State, Nigeria. The study population was HIV positive clients receiving care at the Anti-Retroviral Therapy (ART) clinic. This was a cross-sectional analytical study.

Ethical Consideration

Permission for the study was obtained from the COOUTH Ethical Review Committee.

Confidential in handling patients' data was ensured.

Data management

Clinical information were used to determine WHO clinical staging. Haemoglobin estimation was done. Patients' weight and height were measured and their Body Mass Index (BMI) calculated. Data were analysed using SPSS version 26.0, then evaluated using the various Clinical Prediction Tools.

Clinical Prediction Tools

	Parameters	Score	Interpretation
Primary CPT	Age (years) > 40 ≤ 40	 +2 0	Score range: 0 to 5. The probability of KD ranged from 1.0% for those with a score of 0 to 51.2% for a score of 5. Using a cut-off of the score at 2 (score ≥2), sensitivity for KD was 91.5% in validation, while avoiding testing in 50.5%. Using a higher cut-off (score ≥4) increased specificity as only 7.3% of individuals will require creatinine testing, but with a significant loss in sensitivity.
	Weight (kg) < 45 ≥ 45	 +2 0	
	HB (g/dl) <10 ≥ 10	 +1 0	
	Age (years) > 40 ≤ 40	 +2 0	Replacing body weight with BMI, referred to as the BMI CPT, achieved an AUROC of 0.77 (95%CI 0.72 to 0.83) however sensitivities and specificities were not described.

BMI CPT	BMI (kg/m^2) < 18 ≥ 18	 +2 0	
	HB (g/dl) <10 ≥ 10	 +1 0	
Alternate CPT	Age (years) > 40 ≤ 40	 +2 0	With an alternative risk prediction score which has a 4-item score including age, body weight, sex, and WHO stage, hereafter referred to as the alternate CPT, AUROC was 0.81 (95%CI 0.76 to 0.85). With a cut-off score of ≥2, sensitivity was 95.8%, specificity was 40.7%, and creatinine testing would have been avoided in 37.4% of patients
	Weight (kg) < 45 ≥ 45	 +2 0	
	Sex F M	 +1 0	
	WHO staging 3 & 4 1 & 2	 +1 0	

III. RESULTS

Table 1: Sociodemographic, clinical and laboratory data

Variables	**N=330 n (%)**
Age group (yrs)	
≤ 40	121 (36.7)
>40	209 (63.3)
Sex	
Male	112 (33.9)
Female	218 (66.1)
Weight (kg)	
<45	325 (98.5)
≥45	5 (1.5)
Haemoglobin (g/dl)	
≥10	305 (92.4)
<10	25 (7.6)
Creatinine (mg/dl)	
Normal (Male 0.6-1.3, Female 0.5-1.1)	308 (93.3)
High (Male >1.3, Female >1.1)	22 (6.7)
WHO clinical stage	
1 & 2	319 (96.7)
3 & 4	11 (3.3)
BMI (kg/m^2)	
≥18	320 (97.0)
<18	10 (3.0)

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Evaluation of Clinical Prediction Tools

Table 2 shows the Clinical Prediction Tool score distribution for creatinine of research participants using different tools.

Table 2: Clinical Prediction Tool score for creatinine

Score	Primary CPT n (%)	BMI CPT n (%)	Alternate CPT n (%)
0	108 (32.7)	105 (31.8)	28 (8.5)
1	11 (3.3)	11 (3.3)	87 (26.4)
2	196 (59.4)	197 (59.7)	83 (25.2)
3	12 (3.6)	12 (3.6)	127 (38.5)
4	1 (0.3)	3 (0.9)	2 (0.6)
5	2 (0.6)	2 (0.6)	3 (0.9)
TOTAL	**330 (100.0)**	**330 (100.0)**	**330 (100.0)**

Table 3 shows the proportion of patients in whom creatinine testing can be avoided when these CPT are applied to our patients. Using a cut-off of ≥ 2 for Primary CPT and BMI CPT, 3.3% of our patients will not require creatinine testing before treatment. Using a cut-off of ≥ 2 for Alternate CPT, 26.4% of our patients will not require creatinine testing before treatment. On the other hand, using a cut-off of ≥ 4 for Primary CPT, 95.8% of our patients will not require creatinine testing before treatment.

Table 3: Clinical Prediction Tool cut-off score for creatinine testing

Score	Primary CPT n (%)	BMI CPT n (%)	Alternate CPT n (%)
< 2	11 (3.3)	11 (3.3)	87 (26.4)
≥ 2	319 (96.7)	319 (96.7)	243 (73.6)
Total	**330 (100.0)**	**330 (100.0)**	**330 (100.0)**
< 4	316 (95.8)	314 (95.2)	
≥ 4	14 (4.2)	16 (4.8)	
Total	**330 (100.0)**	**330 (100.0)**	

IV. DISCUSSION

Using risk prediction score that included age, body weight and haemoglobin designated as the primary CPT, the probability of kidney disease ranged from 1.0% in those with a score of 0 to 51.2% in those with a score of 5. With the cut-off score set at ≥ 2, creatinine testing would have been avoided in 50.5% of patients. Using the BMI CPT, replaces weight with BMI. With an alternative risk prediction score which has a 4-item score including age, body weight, sex, and WHO stage, with a cut-off score of ≥2, creatinine testing could have been avoided in 37.4% of patients.(18) Applying these Clinical Prediction Tools to our participants with a cut-off score set at ≥2, creatinine testing could have been avoided in only 3.3% of patients using primary CPT and BMI CPT and in 26.4% using alternate CPT.

With the Alternate Clinical Prediction Tool for kidney function, 26.4% of our patients will not require creatinine testing before commencing HAART. Thus, the preferred CPT because the proportion of patients who will not require creatinine testing is comparable with their prediction. Alternative CPT tool can be considered for adoption by the ART clinic.

Many Clinical Prediction Tools have diagnostic accuracy that are similar to gold standard tests. The gold standard for diagnosing renal artery stenosis, renal angiography, is invasive and costly. However, the diagnostic accuracy of the Clinical Prediction Rule for artery stenosis was found to be similar to that of renal scintigraphy, which had a sensitivity of 72% and a specificity of 90%.(20) Other Clinical Prediction Tools that have been found to be useful are Clinical prediction models in psychiatry(21) and Clinical Prediction Tool for hospital mortality in critically ill elderly patients(22), to mention a few.

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