ORIGINAL ARTICLE

An Assessment of the Accuracy of Creatinine Measurements in Guyana

JL Shaw[1,2,3], YP Irving[4], B Jacobson[5], DW Seccombe[5,6]

ABSTRACT

Background: *The incidence of chronic kidney disease (CKD) is relatively high in Guyana. Estimated glomerular filtration rate (eGFR) reporting allows for early-stage CKD identification when therapeutic interventions can prevent CKD progression. Accurate creatinine measurements are essential for valid eGFR calculations.*

Objective: *This study was undertaken to assess the accuracy of creatinine measurements in Guyana prior to implementing routine eGFR reporting.*

Methods: *Sixteen Guyanese laboratories participated in this study. Each laboratory received a common set of blinded human serum samples (n = 3) containing clinically relevant creatinine concentrations, assigned by an international reference method (ID-GCMS). Laboratories performed repeated measurements of creatinine in each sample. These data were used to calculate bias, precision and total error (TE) for each creatinine method. Linear regression was used to compare measured creatinine results to assigned reference sample values and to post-analytically correct calibration bias, a priori, for recent patient results from each laboratory. Patient eGFR profiles were compared before and after bias correction.*

Results: *The mean across samples CV and bias for all labs were 9% (range 2.5%–39.3%) and 11% positive (range 0.4%–29.1%), respectively. The mean TE was 28.6%. If the mean TE from a subset of the better performing laboratories (CV < 7%) was to apply nationally, an 'all stage' eGFR misclassification rate of 36% would result.*

Conclusion: *There is a pressing need to improve the accuracy of creatinine measurements in Guyana as, at this time, routine reporting of eGFR by Guyanese laboratories cannot be recommended based on the accuracy data presented in this study.*

Keywords: Chronic kidney disease, creatinine, estimated glomerular filtration rate, Guyana, standardization

INTRODUCTION

Chronic kidney disease (CKD) is a major public health problem with increasing prevalence worldwide due to the increased incidence of diabetes and hypertension (1). Left untreated, CKD can progress to end-stage renal disease (ESRD) requiring haemodialysis. Hemodialysis is widely available for the treatment of ESRD in the developed world but this is often not the case in developing countries where a diagnosis of ESRD often results in death (2).

According to a Pan American Health Organization strategy report from 2014 (3), chronic diseases now represent the most significant healthcare challenge in Guyana, surpassing communicable diseases. Each year 8000 new cases of diabetes are diagnosed in this country. It is well recognized that many of these patients will go on to develop kidney disease as an associated

From: [1]Department of Pathology and Laboratory Medicine, The Ottawa Hospital, Ottawa, Canada, [2]Department of Pathology and Laboratory Medicine, University of Ottawa, Ottawa, Canada, [3]Eastern Ontario Regional Laboratories Association, Ottawa, Canada, [4]Qualitest Medical Laboratory, Georgetown, Guyana, [5]CEQAL, Vancouver, Canada and [6]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, Canada.

Correspondence: Dr J Shaw, The Ottawa Hospital and EORLA, 501 Smyth Road, Ottawa K1H 8L6, Ontario, Canada. Email: julshaw@eorla.ca

 DOI: 10.7727/wimj.2015.518

complication of the diabetic disease process. Chronic kidney disease leading to ESRD is a healthcare challenge in Guyana where dialysis is scarcely available and, where available, is often prohibitively expensive for those requiring it. The cost of one dialysis session in Guyana is currently US$52.76 according to the Doobay Medical Centre, Georgetown, Guyana, which operates 24 of the country's 37 available dialysis machines.

Earlier detection of CKD has been shown to optimize care through dietary and lifestyle modifications, leading to better patient outcomes (4, 5). Traditionally, serum creatinine concentrations have been used to monitor renal function. More recently, routine reporting of the estimated glomerular filtration rate (eGFR) has been recommended for the monitoring of renal function by several international organizations. The eGFR is a calculated index that takes into account patient age and gender in addition to serum creatinine concentrations. Most labs have traditionally used the equation developed from the modification of diet in renal disease (MDRD) study to calculate eGFR (6). More recently, a new equation referred to as Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (7) has been introduced and is now the preferred equation for calculating eGFR. This equation more accurately classifies patients with early stage CKD than the MDRD equation.

The Kidney Disease: improving global outcomes (KD-IGO) clinical practice guideline (8) for kidney disease assigns patients to one of six stages of the disease on the basis of a calculated eGFR. Reporting of eGFR and classification of patients based on their calculated eGFR requires standardization of creatinine methods to minimize systemic differences between laboratory methods (9). International initiatives aimed at standardizing creatinine measurements have been undertaken in the developed world (9) but have not been widely implemented throughout the developing world.

The current study was undertaken to assess the accuracy of creatinine measurements in Guyana and to provide an estimation of the potential impact that creatinine standardization could have on the eGFR staging of kidney disease in the Guyanese population.

MATERIALS AND METHODS

Participating laboratories

A total of sixteen laboratories (public and private) agreed on a voluntary basis to participate in the study. A confidentiality agreement was put in place with each laboratory confirming that only aggregated (non-identifying) performance data from the study would be made public. This was necessary to enhance the rate of participation.

Reference samples

Each laboratory received a common set (n = 3) of human serum samples. The creatinine concentrations in these samples were blinded to the end-users and covered the clinical range of interest for the early diagnosis of kidney disease (stage 3). The reference values as assigned by an internationally credentialed reference method for the measurement of this analyte (isotope-dilution mass spectrometry (IDMS) were as follows:

- Sample A—102.7 µmol/L
- Sample B—174.5 µmol/L
- Sample C—139.2 µmol/L

Reference sample analysis

Participating laboratories were asked to measure creatinine in each of the samples three times on each of three days for a total of 27 measurements (nine measurements for each reference sample). The mean of the nine results for each sample was compared to the assigned reference values using linear regression. From these data the within-sample between-day imprecision, the bias and total error of measurement (TE = bias% + 1.65 CV [coefficient of variation]) were calculated for each lab.

Patient data

Each participating laboratory was asked to provide the age, gender and test results for the last 100 reported creatinine results from their lab. These data were used for the calculation of eGFR (CKD-EPI) before and after applying a correction for calibration bias. These calculations provided an estimation of the potential benefit that could be realized from the standardization of the lab's creatinine method.

RESULTS

The various combinations of creatinine methods, reagents and calibrators in-use by the participating laboratories are summarized in Table 1. The majority of the labs were using open heterogeneous methods for the measurement of creatinine. This decision reflected a desire to use less expensive reagents. It is noteworthy that the best overall performing laboratory in the study was using a closed homogeneous testing system.

Table 1: Summary of the instruments used to measure creatinine as well as the methods in-use to measure creatinine in Guyana by participating laboratories

Instrument	Reagents	Calibrators	Method principle
ChemWell	JAS Diagnostics Inc.	Eltron Diagnostic	Jaffe
ChemWell	POINTE Scientific	POINTE Scientific	Jaffe fixed time
ChemWell	Eltron Diagnostic	Eltron Diagnostic	Jaffe kinetic
Reflotron Plus	Roche	Roche	Jaffe kinetic
Envoy 500	Eltron Diagnostic	CHEM-Index	Jaffe kinetic
Biotecnica BT 2000	Eagle Diagnostics	Eagle Diagnostics	Jaffe fixed time
Biotecnica BT 2000	JAS Diagnostics Inc.	JAS Diagnostics Inc.	Jaffe
Biotecnica BT 2000	Eagle Diagnostics	Eltron Diagnostic	Jaffe fixed time
Biotecnica BT 3500	CHEM-Index	CHEM-Index	Jaffe
MC 150	Eltron Diagnostic	Eltron Diagnostic	Jaffe kinetic

Method imprecision

Laboratories measured each reference creatinine sample three times throughout the day on each of three consecutive days. Measurement imprecision was calculated at each creatinine concentration. The average, minimum and maximum CVs at each reference creatinine concentration are presented in Table 2. The average across the sample total measurement error exhibited by each laboratory is presented in Figure together with the lab's average across sample precision.

Method bias

Method bias for each laboratory was calculated by comparing the target value for each reference creatinine sample as assigned by the reference method to the measured creatinine value (mean of nine values) reported by each participating laboratory. The mean% bias (all labs) is presented in Table 3 with the minimum and maximum reported values.

Retrospective eGFR classification of patients in Guyana

Laboratories were asked to submit their most recently reported 100 creatinine test results together with the age and gender of the patient tested. These data were used in calculating the eGFR by the CKD-EPI equation (8) before and after correcting the lab's creatinine method for calibration bias. The impact of calibration bias was determined by comparing the percentage of patients classified within each of the five eGFR categories before and after bias correction of the reported creatinine test result that was used in the calculation. From these data, the percentage of miss-classified patients at each eGFR stage was calculated (Table 4).

Many of the labs were found to be operating methods with very poor precision. In order to provide an estimate of the potential improvement that could be realized from the standardization of creatinine testing in Guyana, a sub-set of the better performing labs (average across sample CV of 7% or less) was selected for this analysis. Nine of the 16 labs were qualified accordingly and only

Table 2: Summary of measurement imprecision for all participating labs

Reference sample	Assigned creatinine concentration (µmol/L) (mg/dL)	Mean CV%	Min CV%	Max CV%
A	(102.7) (1.162)	11.1	2.5	39.3
B	(174.5) (1.974)	7.9	2.5	19.0
C	(139.2) (1.575)	9.1	2.9	21.8

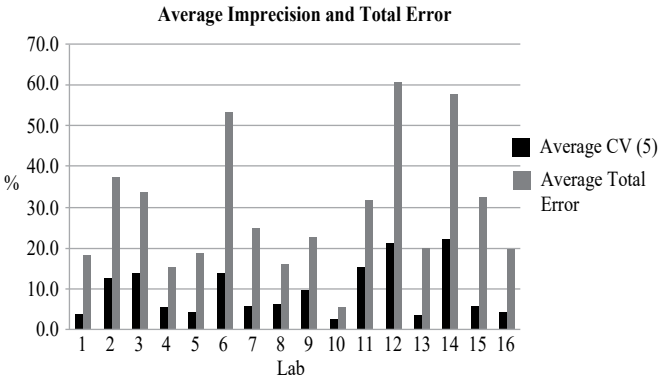

Figure: The average imprecision for each lab over the measurement of three reference creatinine samples was calculated and is shown alongside the average total error for creatinine measurements over three reference creatinine samples.

Table 3: The average, minimum and maximum percentage bias for all participating labs for measurement of each reference creatinine sample

Reference sample	Assigned creatinine concentration (µmol/L) (mg/dL)	Mean bias%	Min bias%	Max bias%
A	(102.7) (1.162)	12.5	0.4	29.1
B	(174.5) (1.974)	10.3	0.5	28.9
C	(139.2) (1.575)	11.5	0.6	27.0

Table 4: The average, minimum and maximum percentages of eGFR-miss-classified patients before and after method bias and imprecision correction for all participating laboratories

Mis-classification %	Stage 5	Stage 4	Stage 3	Stage 2	Stage 1
Average	0.26	1.32	6.98	10.61	17.04
Minimum	0.00	0.00	0.00	0.00	0.00
Maximum	3.00	3.69	24.00	25.49	38.00

eGFR = estimated glomerular filtration rate.

one laboratory was operating a creatinine method with a desirable CV of 2.5%. The 496 patient creatinine test results that had been submitted by this sub-set of labs were subsequently used in the retrospective eGFR staging analysis. Without calibration correction, this subset of labs would have classified 21% of these patients as having stage 3 disease.

Following correction for calibration bias the percentage of patients identified with stage 3 disease decreased to 13%. On a theoretical basis, if the Guyanese population were to be uniformly tested in this group of labs following the standardization of their creatinine methods, 64 000 fewer Guyanese would be identified as having stage 3 kidney disease and therefore in need of follow-up than would be the case if their current methods were used. This reduction in stage 3 false positives would remove the need for follow-up and the added costs to the healthcare delivery system that would be triggered by these test results. In addition, many of the false positives would move to lower risk strata (stages 1 and 2). This would provide opportunities for earlier interventions to prevent the risk of disease and for slowing the rate of disease progression.

DISCUSSION

There are several different instrument types in use in Guyana. The majority are using Jaffe heterogeneous reagent/calibrator systems for the measurement of creatinine. There was only one closed homogeneous system operating in the country. This laboratory had the best overall performance of all the labs studied. Heterogeneous testing systems are less costly but their use introduces many confounding factors that have a negative impact on the overall quality and accuracy of the creatinine test results produced. This was certainly a contributing factor to the high error rates observed in this study.

Measurement imprecision was a significant problem for the majority of the labs. Only two of the labs were operating systems that were precise enough to warrant standardization. Onsite investigations of lab practice identified a number of factors that would have a negative impact on precision. Paramount among these was the poor environmental control that was being exercised for maintaining the temperature and humidity in the lab at acceptable levels as required for the optimal performance of the method and the analyzer. Although the majority of labs were operating internal quality control systems, these systems were not being used properly for monitoring the performance of their creatinine method. Method performance was being monitored on the basis of the manufacturer's suggested performance targets and ranges as opposed to those established on the basis of 'in house' method performance. This would essentially preclude the identification of significant changes in performance.

The majority of the labs in this study were operating creatinine methods with a positive calibration bias, a reality that would significantly increase the number of false positives with population-based eGFR screening. There was no evidence that the calibrator set points were traceable to internationally recognized standards for the measurement of creatinine and most of the labs were using a single point calibration curve that was being forced through zero.

The patient test result data from each lab were used to retrospectively calculate the eGFR that the laboratory would have reported on the basis of the performance of their current creatinine method. The eGFR was then re-calculated for these patients after the lab's creatinine method had been corrected for calibration bias. The calculated eGFR values before and after correction for calibration bias were compared. The correction for calibration bias decreased the number of miss-classified patients in all stages of renal disease. This was not surprising in light of the positive bias that was observed in the majority of the labs that participated in this study.

Efforts to standardize creatinine methods have been implemented in the developed world and have allowed for accurate eGFR calculations. Previous to standardization, these creatinine methods too showed significant bias demonstrating that the need for standardization is not unique to the developing world. A recent study by Killeen *et al* analysed the performance of creatinine methods throughout the United States between 2003 and 2011 based on College of American Pathologist proficiency testing data (9). They demonstrated that prior to standardization efforts, significant method bias existed, ranging from 7% to + 34% in 2003. In 2011, the bias for methods ranged from –5% to +10%, showing marked improvement.

Here, we present the performance of creatinine methods in-use in a mixture of private and public diagnostic laboratories in Guyana. These methods show significant imprecision as well as method bias when compared to values assigned by the IDMS reference method. If left uncorrected, the magnitude of analytical error for the measurement of creatinine in Guyana would result in a significant number of Guyanese being incorrectly classified on the basis of their lab reported eGFR test results.

Currently, in Guyana, patients are identified as having chronic kidney disease only once it has progressed to end-stage renal failure requiring dialysis. Data from the Doobay Renal Centre in Georgetown Guyana estimate that only 1.5% of the population who require dialysis are receiving treatment. Dialysis is only available in the capital city, Georgetown.

Strategies aimed at improving the precision of laboratory creatinine methods followed by standardization efforts to improve method bias will be needed for the laboratories in Guyana to report accurate eGFR results. Achieving this goal will be essential for clinicians in Guyana to accurately identify CKD in their patients and to provide their 'at risk' patients with guidance on diet and lifestyle modifications aimed at preventing or slowing progression of their disease.

The economic impact of inaccurate lab tests on health care delivery systems is seldom a topic of discussion in peer-reviewed publications. In light of the limited resources and the scarcity of funds for healthcare delivery in Guyana, the question should be asked as to whether or not it would be cost-effective to standardize the measurement of creatinine in the country.

The standardization of creatinine testing could be achieved through the use of accuracy based internal quality control samples (three levels) that would be analyzed once a week for improving and monitoring the accuracy of the lab's creatinine testing method. The estimated cost per lab for such a programme would be approximately USD$4500. Providing this quality control system to the 16 laboratories in this study would cost USD$72 000 per year. The estimated per patient yearly cost for dialysis treatment (three sessions per week) in Guyana is USD$8230. For the creatinine standardization programme to pay for itself (return on investment), nine at-risk patients would have to be identified and kept from needing dialysis for one year. This analysis does not include the additional benefits to be derived from the standardization of creatinine testing and the beneficial impact that this would have on identifying at-risk patients earlier in their disease process and thereby optimizing the opportunity for introducing interventions aimed at slowing and/or preventing progression of their disease to end stage.

ACKNOWLEDGEMENTS

This project was funded by Grand Challenges of Canada. We would like to thank all the laboratories in Guyana who participated in this study.

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