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Effect of creatinine and cystatin C measurement variations on calculated estimated glomerular filtration rate variations and the theoretical impact on kidney disease stage classification: A retrospective study

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ABSTRACT

Background: The estimated glomerular filtration rate (eGFR) is an important parameter in the management of patients with kidney diseases, yet eGFR quality goals are lacking. We examined the uncertainties in eGFR determinations and assessed their impact on patient classifications, aiming to set eGFR quality goals.

Methods: Adult patients undergoing creatinine concentration assessments at our hospital, between June 2014 and October 2016, were included (N = 285,982). Using 7 eGFR equations, we calculated the imprecisions in the eGFR, based on the imprecisions in determining creatinine and/or cystatin C concentrations. The uncertainties in the eGFR were expressed as functions of creatinine and/or cystatin C concentration uncertainties. Subsequently, the number of ambiguous cases was assessed, based on the calculated uncertainty in the eGFR.

Results: Uncertainties in the eGFRs varied according to the eGFR calculation equation used. Although a 0.8% expanded uncertainty in the eGFR caused a 3.5% ambiguous case rate, a 10% expanded uncertainty resulted in a 42.3% rate of ambiguous cases. To meet minimal quality requirements, creatinine imprecision should be ≤ 3.0%.

Conclusions: Even a low level of uncertainty in the eGFR may cause noticeable impacts on patient classifications. Laboratory physicians should be aware, and cautious, of the uncertainties in eGFR calculations.

1. Introduction

Appropriate quality control in clinical laboratories is essential for proper patient management. The Stockholm consensus statement issued in 1999 by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and its revised version, the Milan consensus statement of 2014, both state that using quality goals derived from clinical outcomes is ideal [1,2]. However, few items can meet this ideal. Therefore, quality goals derived from biological variation (BV) have been underscored as attractive and practical alternatives.

Creatinine concentration is the most popular biomarker for assessing kidney function, and has been used extensively in clinical practice. Given the great importance of a strict quality control for creatinine, the National Kidney Disease Education Program (NKDEP) has suggested a quality goal based on BV [3]. In this recommendation, the minimum requirement for creatinine concentration imprecision is ≤ 3.2% and the optimum is ≤ 1.1%. However, creatinine concentrations are determined using pre-analytical variables (e.g., sex, age, diet, muscle mass, etc.), rather than renal function itself [4]. Thus, cystatin C concentrations have been used as substitutes; however, its concentration can be influenced by various factors, such as thyroid dysfunction [5]. Therefore, renal function is usually assessed using the estimated glomerular filtration rate (eGFR) [6]. Numerous studies exist regarding the calculation of the eGFR using creatinine and/or cystatin C concentrations [7–11]. The two most widely used equations are the 4-variable Modification of Diet in Renal Disease (MDRD) equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Full age spectrum (FAS) equation has been recently introduced and has drawn attention due to its wide age applicability [12]. Although the eGFR should be considered, as well as creatinine and/or cystatin C concentrations, the current procedures for laboratory quality control have focused on the imprecision of the analytes, which is partly due to the of available strategies to monitor imprecision in the eGFR calculation. In addition, proposals regarding eGFR quality goals are lacking. Therefore, in the present study, we calculated the imprecision in the eGFR based on the imprecision in creatinine and/or cystatin C

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assessments (using various eGFR calculation equations). In addition, we examined the impact of eGFR imprecision on the classification of real patients, with the aim of setting eGFR quality goals.

2. Materials and methods

This study was approved by the Institutional Review Board of Dongtan Sacred Heart Hospital (2017-05-316-001).

2.1. eGFR equations

Diverse equations are available for calculating eGFR using creatinine and/or cystatin C concentrations. The following 7 equations were used in this study [7–12].

1) Cockcroft-Gault equation: $CrCL = ((140 - Age) \times Weight) / (72 \times S_{Cr}) \times (0.85, \text{ if female})$
2) 4-variable MDRD equation (IDMS-traceable): $eGFR = 175 \times (S_{Cr})^{-1.154} \times (Age)^{-0.203} \times (0.742, \text{ if female}) \times (1.212, \text{ if of African descent})$
3) CKD-EPI equation (2009): $eGFR = 141 \times \min(S_{Cr} / \kappa, 1)^{\alpha} \times \max(S_{Cr} / \kappa, 1)^{-1.209} \times 0.993^{Age} \times (1.018, \text{ if female}) \times (1.159, \text{ if of African descent})$
4) Bedside Schwartz equation: $eGFR = 41.3 \times (Height / S_{Cr})$
5) CKD-EPI Cystatin C equation (2012): $133 \times \min(S_{cys} / 0.8, 1)^{-0.499} \times \max(S_{cys} / 0.8, 1)^{-1.328} \times 0.996^{Age} \times (0.932, \text{ if female})$
6) CKD-EPI Creatinine-Cystatin C equation (2012): $eGFR = 135 \times \min(S_{Cr} / \kappa, 1)^{\beta} \times \max(S_{Cr} / \kappa, 1)^{-0.601} \times \min(S_{cys} / 0.8, 1)^{-0.375} \times \max(S_{cys} / 0.8, 1)^{-0.711} \times 0.995^{Age} \times (0.969, \text{ if female}) \times (1.08, \text{ if of African descent})$
7) FAS equation: $eGFR = 107.3 / (S_{Cr} / Q) \times (0.988^{(Age - 40)}, \text{ if } age > 40 \text{ years})$

Creatinine clearance (CrCL) was measured in mL/min. The eGFR was calculated as mL/min/1.73 m^2. Patient ages were measured in years and weights were measured in kg. Serum creatinine concentration (S_{Cr}) was measured in mg/dL, whereas the serum cystatin C concentration (S_{cys}) was measured in mg/L. The indicated values were used for $\kappa = 0.7$ (women) or 0.9 (men); $\alpha = -0.329$ (women) or -0.411 (men); $\beta = -0.248$ (women) or -0.207 (men); min(A, B) indicates the minimum of A or B, and max(C, D) = indicates the maximum of C or D; and Q indicates the median serum creatinine value for age-/sex-specific healthy populations. IDMS means isotope-dilution mass spectrometry.

2.2. Estimation of eGFR uncertainty

Uncertainty calculations, based on functional relationships, are well-established processes for error propagation and uncertainty estimation [13]. Among the parameters in the above equations, only creatinine and cystatin C concentrations are considered to be variables having uncertainty. Using the rules for the evaluation of standard uncertainty, we calculated the uncertainty budget in the eGFR as a function of the uncertainties in creatinine and/or cystatin C concentrations.

Measurement uncertainty can be expressed as experimental standard deviations (SDs) [14]. The analytical imprecision in each assay can be considered to be representative of the standard uncertainty. Similarly, coefficient of variance (CV) can be considered as a representative of fractional uncertainty. Expanded uncertainty was computed by multiplying the coverage factor of 2, which corresponds to 95% confidence interval (CI) [14].

For each equation, we assessed the relationship between the uncertainty in creatinine and/or cystatin C concentrations and the uncertainty in the eGFR. Expanded uncertainty in the eGFR was estimated for the currently recommended BV-derived quality goals for creatinine and/or cystatin C assessments. Creatinine imprecision goals were those suggested by NKDEP (minimal, desirable, and optimal fractional uncertainties (CVs) of 3.2%, 2.2%, and 1.1%, respectively) [3]. Quality requirements for cystatin C were estimated from the most current version of the BV database (minimal, desirable, and optimal CVs of 3.8%, 2.5%, and 1.3%, respectively) [15,16].

2.3. Impact of uncertainty in the eGFR on patient classification

Adult patients (≥ 18-years-old) who underwent creatinine assessments at the Dongtan Sacred Heart Hospital, between June 2014 and October 2016, were included. Creatinine concentrations were assessed using Jaffe method in automated analyzers (CREJ2 c702, Roche Diagnostics, Basel, Switzerland or Toshiba 2000FR, Toshiba Medical Systems, Tokyo, Japan). Both methods used are traceable to isotope dilution-mass spectrometry, and the comparability between the two instruments is assessed biannually using fresh patient samples. For each patient, the eGFR was calculated using the CKD-EPI equation (2009), followed by categorization according to the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines as follows [6]: normal or high (≥ 90 mL/min/1.73 m^2), mildly decreased (60–89 mL/min/1.73 m^2), mildly to moderately decreased (45–59 mL/min/1.73 m^2), moderately to severely decreased (30–44 mL/min/1.73 m^2), severely decreased (15–29 mL/min/1.73 m^2), and kidney failure (< 15 mL/min/1.73 m^2).

The 95% CIs for the calculated eGFR were computed using the expanded uncertainty, as explained above [14,17]. If the 95% CI included the boundary for categorization, the case was classified as ambiguous. The number of ambiguous cases derived from the uncertainty in the eGFR was evaluated, and the required goals to limit the proportion of ambiguous cases to < 3%, 12%, and 25% (in accordance with the quality requirements for BV [15,16]) were determined.

3. Results

3.1. Estimation of eGFR uncertainty

The results of the error propagation and uncertainty estimations are shown for each eGFR equation in Table 1. For Cockcroft-Gault equation, Bedside Schwartz equations, and FAS equation, the CV in the eGFR was the same as that for creatinine. The maximal CV in the eGFR was 1.209-times that for creatinine using the CKD-EPI equation (2009), and was 1.328-times that for cystatin C using the CKD-EPI Cystatin C equation (2012). For the combined equation (using both the creatinine and cystatin C concentrations), the maximum fractional uncertainty occurred in women with elevated creatinine (> 0.7 mg/dL) and cystatin C (> 0.8 mg/L) concentrations.

3.2. Assessment of uncertainty in the eGFR and establishment of quality goals

The estimated maximal CV in the eGFR at different analyte imprecision levels (in accordance with BV quality requirements) is shown in Table 2. The CKD-EPI Cystatin C equation (2012) had the highest level of uncertainty, compared with those for other formulas. Interestingly, the relatively old and simple equations (i.e., the Cockcroft-Gault and Bedside Schwartz equations) had lower uncertainties in the calculated eGFRs than did those using the more recent equations (i.e., the MDRD and CKD-EPI equations (2009)). Although the CKD-EPI Creatinine-Cystatin C equation (2012) requires two variables as inputs, it had the lowest uncertainty.

3.3. Application to patient data

A total of 285,982 creatinine tests were collected during the study period, and the patient classification distribution is shown in Table 3. Surprisingly, even a small uncertainty in the eGFR induced a great