Comparison of Equations To Estimate Glomerular Filtration Rate and Their Impact on Frequency of Cisplatin-associated Acute Kidney Injury

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Abstract

Background Accurate estimation of kidney function is essential for patient selection and drug dosing in patients with cancer. eGFR equations are necessary for decision making and monitoring. Our aim was to identify which of these equations—estimated creatinine clearance (eCrCl) by Cockcroft-Gault (CG), eGFR by Modification of Diet in Renal Disease (eGFRMDRD), CKD Epidemiology Collaboration (eGFRCKD-EPI) or the recently proposed Janowitz-Williams equation (eGFRJ-W)—would be most suitable for GFR estimation among patients with cancer receiving cisplatin.

Methods We assembled a cohort of 5274 patients with cancer treated with cisplatin-based chemotherapy at two large cancer centers. We ascertained the frequency of cisplatin-associated AKI (C-AKI) defined as a $0.3 \text{mg/dl}$ rise in serum creatinine over baseline. We compared baseline eGFR and eCrCl using Bland-Altman (B-A) plots, coefficients of variation (CV), and concordance correlation coefficients. We calculated the positive predictive value (PPV), negative predictive value (PPV), accuracy, and area under the curve (AUC).

Results Patients were predominantly middle aged (median 58 years, IQR 49–66 years), overweight (median BMI 26.2, IQR 23.1–29.8 kg/m²), and White (88%), with a median baseline creatinine of 0.8 mg/dl and median cisplatin dose of 99 mg. C-AKI developed in 12% of the cohort. eGFRCKD-EPI had the highest PPV and AUC. eGFRCKD-EPI and eGFRMDRD, along with their BSA-modified counterparts, had the closest agreement with the lowest CV (7.2, 95% CI, 7.0 to 7.3) and the highest concordance. C-AKI was lowest when using eGFRCKD-EPI to define eGFR $\geq 60 \text{ml/min per 1.73m}^2$.

Conclusions On the basis of its superior diagnostic performance, eGFRCKD-EPI should be used to estimate GFR in patients being considered for cisplatin-based chemotherapy.

Introduction

Cisplatin remains the backbone of several cytotoxic chemotherapy regimens five decades since its discovery, despite a rapid rate of introduction of novel chemotherapeutics in oncology (1). Toxicity remains the major drawback of its use and is strongly associated with the dose administered (2). Dosing may vary from cycle to cycle, due to several clinical considerations, one of which may be kidney function (3,4). Because cisplatin is cleared by the kidney (>90%), an accurate estimate of kidney function is essential.

There is considerable heterogeneity in clinical practice for assessing kidney function. Different methods including serum creatinine (sCr), estimation of creatinine clearance (eCrCl) by the Cockcroft-Gault (CG) equation, and GFR (eGFR)-estimating equations by either the Modification of Diet in Renal Disease (eGFRMDRD) or CKD Epidemiology Collaboration (eGFRCKD-EPI) are in use. In addition, a new equation for estimation of GFR using data from patients who received carboplatin was recently proposed (5). The gold standard is direct measurement of the GFR; however, measurement of GFR is cumbersome. Thus, eGFR equations, in addition to sCr, are the mainstay for evaluating kidney function in the clinical setting.

One reason for the relative popularity of the eGFRCKD-EPI equation among nephrologists is its higher accuracy, at GFR $\geq60 \text{ml/min per 1.73 m}^2$ (2,6,7), a level above which most patients receiving cisplatin would fall. However, eGFRCKD-EPI is still not widely utilized by oncologists for making treatment decisions (4). Barriers to adopting eGFRCKD-EPI are not entirely clear, but may include the absence of high-quality evidence and the use of other formulae in...
the literature. Data are needed from cohorts with a large sample size, and those not limited by cancer type or dose ranges. To address this gap in the literature, we assembled a cohort of over 5000 patients treated with cisplatin-based chemotherapy. We evaluated the differences in risk of developing cisplatin-associated AKI (C-AKI), by retrospectively applying various equations for estimating baseline kidney function among patients in this cohort.

**Materials and Methods**

**Study Population**

We conducted an observational study of patients treated with cisplatin at Massachusetts General Hospital or Dana-Farber Cancer Institute (DFCI)/Brigham and Women’s Cancer center between the years 2000 and 2015. We assembled this cohort using information from two large patient data repositories and from the individual hospital pharmacies: (1) Partners Research Patient Data Registry, which collects data from all Partners-affiliated institutions including Massachusetts General Hospital and Brigham and Women’s Hospital, and (2) DFCI’s Oncology Data Retrieval System (OncDRS). The study was approved by the Institutional Review Board. This approval included a complete ethics review of data procurement, storage, and use.

We included patients 18 years of age or older, treated with cisplatin, who had at least one sCr measurement within the month before the first course of cisplatin and at least one measurement within 14 days after the first course. Patients with a missing height or weight, or those who had cisplatin administered in the setting of allergic desensitization were excluded. We did not exclude patients at extremes of weight (below the 2.5th and above 97.5th percentile), because our goal was to compare various equations with each other because they related to the frequency of C-AKI, rather than arriving at an accurate value of eGFR in comparison with measured GFR.

We collected data from the month before the date of an individual’s first course of cisplatin (“index date”). Demographic information collected included age, sex, race, height, and weight at the time of initial cisplatin administration. Clinical information collected included cisplatin dose, date of infusion, serum BUN, and creatinine; and history of diabetes or hypertension recorded before the index date using diagnosis codes.

**Equations to Estimate Renal Function**

We calculated the eCrCl (8), eGFR (5,9,10), and body surface area (BSA) (11) and BSA-modified estimates for all patients in the study using the following equations:

### eCrCl by CG

\[
CG \text{ eCrCl } ml/min = [(140 - \text{age}) \times \text{weight}] \div (\text{sCr} \times 72)
\]

### eGFR by MDRD

\[
eGFR_{MDRD} (ml/min per 1.73 m^2) = 175 \times (\text{Scr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if Black})
\]

### eGFR by CKD-EPI

\[
eGFR_{CKD-EPI}(ml/min per 1.73 m^2) = 141 \times \min (\text{Scr}/\kappa, 1)^{\alpha} \times \max (\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if Black]}
\]

where:

- $\text{Scr}$ is in mg/dl, $\kappa$ is 0.7 for females and 0.9 for males, $\alpha = -0.329$ for females and $-0.411$ for males, min indicates the minimum of $\text{Scr}/\kappa$ or 1, and max indicates the maximum of $\text{Scr}/\kappa$ or 1.

### eGFR\textit{J-W} by Janowitz-Williams (J-W eGFR)

\[
\sqrt{GFR} = \beta_0 + \beta_1 \text{Age} + \beta_2 \text{BSA} + \beta_3 \ln(\text{Cre}) + \beta_4 \ln(\text{Cre})^2 + \beta_5 \ln(\text{Cre})^3 + (\beta_6 + \beta_7 \text{Age}) \{\text{if Sex} = \text{M}\} + \beta_8 \text{Age} \times \text{BSA} + \epsilon
\]

### Estimated BSA by Du Bois and Du Bois

\[
\text{BSA} (m^2) = (W^{0.425} \times H^{0.725}) \times 0.007184
\]

\[
W \text{ weight (kg), } H \text{ height (cm)}
\]

BSA-based drug dosing is a common convention in oncology practice (12,13). We wanted to evaluate if modifying the estimate to the patient’s individual BSA has an effect on the association. At the time of derivation, eGFR\textit{CKD-EPI} and eGFR\textit{MDRD} were indexed to BSA (11), but CG eCrCl was not. eGFR-estimating equations are indexed to a BSA of 1.73 m\textsuperscript{2} because that was the average BSA in young adults when indexing was first introduced. Therefore, we performed the BSA modifications of eGFR equations as follows:

\[
\text{CKD-EPI}_{\text{BSA}} = \text{eGFR}_{\text{CKD-EPI}} \times (\text{BSA}/1.73)
\]

\[
\text{MDRD}_{\text{BSA}} = \text{eGFR}_{\text{MDRD}} \times (\text{BSA}/1.73)
\]

Where BSA is the individual patient’s BSA calculated as shown above.

### Outcome

We defined C-AKI as a $\geq 0.3$ mg/dl rise in sCr from baseline to peak measurement after the first course of cisplatin, in accordance with the National Cancer Institute’s nephrotoxicity criteria (14). Creatinine closest to the cisplatin exposure checked within the month before the index date was used as the baseline. Peak creatinine was defined as the highest creatinine value within 14 days after the index date.

### Statistical Analyses

Continuous variables are presented as mean (SD) or median (interquartile range), whereas categorical variables are described by frequency. Unadjusted associations between the covariates and the primary outcome were
evaluated using chi-squared tests for categorical data, the chi-squared test for normally distributed variables, and the Kruskal-Wallis test for nonparametric variables. C-AKI frequencies between groups were compared using Fisher's exact test. Bland-Altman (B-A) plots were constructed for assessing agreement between various equations. We also calculated the coefficient of variation (CV) and correlation coefficients (CC). Using each equation, we calculated the positive predictive value (PPV) of diagnosing C-AKI at an eGFR <60 ml/min and negative predictive value (NPV) of excluding C-AKI at an eGFR ≥ 60 ml/min. We then calculated the accuracy of each equation and compared the area under the curve (AUC) by the DeLong test (16) using C-AKI as the outcome. A two-sided P value of <0.05 was considered significant. Analyses were performed using SAS version 9.4. (SAS Institute, Cary, NC) and Medcalc version 17.9.7 (Medcalc software bvba, Belgium).

Results

We identified 6616 patients who received cisplatin and had at least one baseline creatinine measurement in our system. For simplicity, all of the units are presented as ml/min unless otherwise noted. After excluding those with missing height or weight (n = 228) and patients with extreme values for eGFR or eCrCl (defined as >200 ml/min, n = 138), 6250 patients remained. Of these, 5274 patients had a follow-up creatinine value within 14 days of cisplatin exposure and were included in the analysis.

Clinical characteristics of patients overall and by C-AKI status are shown in Table 1. Patients were predominantly of male sex (57%) and White race (88%), with a median age of 58 years (interquartile range [IQR] 49–66 years) and body mass index of 26.2 kg/m² (IQR 23.1–29.8 kg/m²). Many had hypertension (38%), fewer had diabetes (13%), and the median baseline creatinine was 0.8 mg/dl (IQR 0.7–1.0 mg/dl). The majority of patients (84%) had the baseline creatinine measured in the same encounter as cisplatin administration.

The median time between the baseline creatinine measurement and administration of cisplatin was 0 (IQR 0, 0 days). The median cisplatin dose was 99.0 mg (IQR 60.1–143.5 mg). C-AKI developed in 606 of the 5274 patients (12%).

PPV of C-AKI in patients with eGFR or eCrCl <60 ml/min was overall low for all equations (13%–18%) as a stand-alone measure for prediction of C-AKI. However, among the equations, it was the highest for eGFR_{CKD-EPI} and lowest for J-W eGFR. NPV for eGFR or eCrCl ≥ 60 ml/min was high and nearly equal for all equations (89%) (Table 2). The accuracy was the highest for J-W eGFR despite its lowest PPV and NPV values. This was likely because it was affected by the proportion of true negatives, and was skewed toward equations estimating the highest value of eGFR.

We also estimated AUC for individual equations with C-AKI as the outcome and compared various equations by the DeLong test (16). The AUC for predicting C-AKI was significantly higher for eGFR_{CKD-EPI} (AUC 0.59, 95% confidence interval [95% CI], 0.57 to 0.60, P<0.0001) compared with the other equations (Table 3).

Comparison of Various Equations

We constructed B-A plots to examine the agreement between various equations as shown in Figure 1. The best

Table 1. Clinical characteristics of the study population

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>All Patients (n=5274)</th>
<th>Cisplatin-associated AKI (n=606; 11.5%)</th>
<th>No Cisplatin-associated AKI (n=4668)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, in yr, median (IQR)</td>
<td>58.0 (49–66)</td>
<td>63 (55, 69)</td>
<td>58 (49, 65)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>57</td>
<td>67.8</td>
<td>55.6</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (%)</td>
<td>88</td>
<td>90</td>
<td>87</td>
</tr>
<tr>
<td>Black (%)</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Others (%)</td>
<td>9</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>38</td>
<td>52</td>
<td>36</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>13</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Baseline creatinine, mg/dl, median (IQR)</td>
<td>0.8 (0.7–1.0)</td>
<td>0.9 (0.7–1.0)</td>
<td>0.8 (0.7–1.0)</td>
</tr>
<tr>
<td>Height, cm, median (IQR)</td>
<td>169.6 (162.5–176.5)</td>
<td>171.5 (164.0–177.6)</td>
<td>169.3 (162.2–176.3)</td>
</tr>
<tr>
<td>Weight, lbs, median (IQR)</td>
<td>167.4 (141.0–194.7)</td>
<td>178.1 (149.8–205.9)</td>
<td>166.1 (140.0–192.9)</td>
</tr>
<tr>
<td>BMI, kg/m², median (IQR)</td>
<td>26.2 (23.1–29.8)</td>
<td>27.6 (24.0–31.1)</td>
<td>26.0 (23.0–29.6)</td>
</tr>
<tr>
<td>BSA, m², median (IQR)</td>
<td>1.9 (1.7–2.0)</td>
<td>1.9 (1.8–2.1)</td>
<td>1.9 (1.7–2.0)</td>
</tr>
<tr>
<td>Cisplatin dose, mg, median (IQR)</td>
<td>99.0 (60.1–143.5)</td>
<td>135.5 (72.0–176.0)</td>
<td>94.8 (59.5–140.0)</td>
</tr>
<tr>
<td>Measures of eGFR and eCrCl median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR_{CKD-EPI} ml/min per 1.73 m²</td>
<td>91 (77–102)</td>
<td>86.4 (70.9–98.5)</td>
<td>91.9 (77.4–102.1)</td>
</tr>
<tr>
<td>CKD-EPI_{BSA}, ml/min</td>
<td>97 (81–112)</td>
<td>81.5 (67.6–100.4)</td>
<td>85.5 (72.4–100.4)</td>
</tr>
<tr>
<td>eGFR_{MDRD} ml/min</td>
<td>85 (72–100)</td>
<td>93.5 (71.5–120.8)</td>
<td>98.4 (78.2–122.4)</td>
</tr>
<tr>
<td>MDRD_{BSA}, ml/min per 1.73 m²</td>
<td>92 (76–110)</td>
<td>93.5 (75.9–111.7)</td>
<td>97.0 (82.0–112.1)</td>
</tr>
<tr>
<td>CG eCrCl, ml/min</td>
<td>98 (78–122)</td>
<td>90.2 (72.4–111.7)</td>
<td>92.5 (76.8, 110.2)</td>
</tr>
<tr>
<td>J-W eGFR, ml/min</td>
<td>98 (78–122)</td>
<td>90.4 (76.7–107.0)</td>
<td>92.2 (79.3–106.7)</td>
</tr>
</tbody>
</table>

IQR, interquartile range; BMI, body mass index; BSA, body surface area; eCrCl, creatinine clearance; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CKD-EPI_{BSA}, CKD-EPI (patient’s BSA/1.73); MDRD, Modification of Diet in Renal Disease; MDRD_{BSA}, MDRD × (patient’s BSA/1.73); CG CrCl, Cockcroft-Gault creatinine clearance; J-W eGFR, Janowitz-Williams eGFR.
agreement was between eGFR_{CKD-EPI} and eGFR_{MDRD} values, with a small positive bias of 1.7 (95% CI, -18.2 to 21.6). The worst agreement was between MDRD and CG CrCl (bias -14.0; 95% CI, -63.4 to 35.4). For all equations, the B-A plots demonstrated the agreement was best at lower kidney function values. To examine the disparity, the CV and CC plots demonstrated the agreement was best at lower kidney function values. The eGFR_{CKD-EPI} and eGFR_{MDRD} and their BSA-modified counterparts had the lowest CV (7.2; 95% CI, 7.0 to 7.3) and highest CC (88%, 95% CI, 87% to 88%; and 90%, 95% CI, 90% to 91%, respectively), whereas CG CrCl had a very high CV when compared with either eGFR_{CKD-EPI} (19.3, 95% CI, 19.8 to 19.7) or eGFR_{MDRD} (21.8, 95% CI, 21.4 to 22.3) and a very low concordance (55%, 95% CI, 53% to 56% and 54%, 95% CI, 52% to 55%, respectively) (Table 4). The results did not materially change after stratifying the analyses by cisplatin dose above and below the median (data not shown).

Risk Categories
Using a threshold of 60 ml/min for kidney function impairment commonly used in clinical practice, we classified the patients by eGFR or eCrCl ≥60 ml/min and <60 ml/min. Patients with eGFR ≥60 ml/min were deemed “lower risk” and <60 ml/min “higher risk” for C-AKI. On the basis of this classification, the number of patients who were lower risk was calculated to be the highest for J-W eGFR (95%), followed by CKD-EPI_{BSA} (94%), eGFR_{MDRD} (92.2%), MDRD_{BSA} (92.2%), CG CrCl (91.8%), and MDRD (90.2%). We further calculated C-AKI frequencies in each of these hypothetical lower- and higher-risk groups (Table 2). eGFR_{CKD-EPI} had significantly fewer patients with C-AKI in the higher- compared with the lower-risk group (11% versus 18%, P<0.0001), suggesting beneficial dichotomization; followed by MDRD (11% versus 16%, P=0.0006) and CKD-EPI_{BSA} (11% versus 15%, P=0.04). We investigated whether the C-AKI frequency in the higher risk group was due to a higher cisplatin dose and that in the lower risk group due to a lower cisplatin dose. However, that was not the case. Cisplatin dose was substantially lower among patients in the higher-risk group compared with patients in the lower-risk group. This finding was confirmed by bivariable regression analysis, in which weight was added as the second independent variable in the model. The analysis showed that a lower eGFR or eCrCl was associated with a lower cisplatin dose independent of weight (Supplemental Table 1). C-AKI frequency was no different between patients in the lower risk versus higher risk groups using MDRD_{BSA}, CG CrCl, CG CrCl_{BSA}, and the J-W eGFR equations.

<table>
<thead>
<tr>
<th>Method</th>
<th>n/N (%)</th>
<th>&gt;60 ml/min (Higher Risk)</th>
<th>n/N (%)</th>
<th>&gt;60 ml/min (Lower Risk)</th>
<th>n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR_{CKD-EPI}</td>
<td>412/5274 (8)</td>
<td>74/412 (18)</td>
<td>532/4862 (11)</td>
<td>&lt;0.0001</td>
<td>18</td>
</tr>
<tr>
<td>CKD-EPI_{BSA}</td>
<td>321/5274 (6)</td>
<td>49/321 (15)</td>
<td>557/4953 (11)</td>
<td>0.04</td>
<td>15</td>
</tr>
<tr>
<td>eGFR_{MDRD}</td>
<td>518/5274 (10)</td>
<td>84/518 (16)</td>
<td>522/4756 (11)</td>
<td>0.0006</td>
<td>16</td>
</tr>
<tr>
<td>MDRD_{BSA}</td>
<td>55/412 (13)</td>
<td>0.23</td>
<td>13</td>
<td>89</td>
<td>83</td>
</tr>
<tr>
<td>CG eCrCl</td>
<td>431/5274 (8)</td>
<td>58/431 (14)</td>
<td>548/4843 (11)</td>
<td>0.18</td>
<td>14</td>
</tr>
<tr>
<td>J-W eGFR</td>
<td>257/5274 (5)</td>
<td>32/257 (13)</td>
<td>574/5017 (11)</td>
<td>0.62</td>
<td>13</td>
</tr>
</tbody>
</table>

Positive predictive value of C-AKI among those at higher risk. Negative predictive value of absence of C-AKI among patients at lower risk. C-AKI, Cisplatin-associated AKI; CKD-EPI, CKD Epidemiology Collaboration; CKD-EPI_{BSA}, CKD-EPI × (patient’s body surface area [BSA]/1.73); MDRD, Modification of Diet in Renal Disease; MDRD_{BSA}, MDRD × (patient’s BSA/1.73); CG CrCl, Cockcroft-Gault creatinine clearance; J-W eGFR, Janowitz-Williams eGFR.

Table 3. Area under the curve for various equations with cisplatin-associated AKI as the classifier

<table>
<thead>
<tr>
<th>Equations</th>
<th>Area Under the Curve</th>
<th>95% Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR_{CKD-EPI}</td>
<td>0.59</td>
<td>0.57 to 0.60</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CKD-EPI_{BSA}</td>
<td>0.54</td>
<td>0.52 to 0.55</td>
<td>0.003</td>
</tr>
<tr>
<td>eGFR_{MDRD}</td>
<td>0.56</td>
<td>0.54 to 0.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MDRD_{BSA}</td>
<td>0.52</td>
<td>0.51 to 0.53</td>
<td>0.16</td>
</tr>
<tr>
<td>CG eCrCl</td>
<td>0.54</td>
<td>0.52 to 0.55</td>
<td>0.005</td>
</tr>
<tr>
<td>J-W eGFR</td>
<td>0.52</td>
<td>0.51 to 0.53</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Areas under the curve (AUCs) for predicting C-AKI using various equations are reported above. All comparisons between the reported AUCs are statistically significant except between CKD-EPI_{BSA} compared with CG eCrCl and MDRD_{BSA} compared with J-W eGFR. C-AKI, Cisplatin-associated AKI; CKD-EPI, CKD Epidemiology Collaboration; CKD-EPI_{BSA}, CKD-EPI × (patient’s body surface area [BSA]/1.73); MDRD, Modification of Diet in Renal Disease; MDRD_{BSA}, MDRD × (patient’s BSA/1.73); CG CrCl, Cockcroft-Gault creatinine clearance; J-W eGFR, Janowitz-Williams eGFR.
Figure 1. Bland-Altman plots comparing agreement between eGFR_{CKD-EPI}, eGFR_{MDRD}, CG CrCl, and their BSA-modified counterparts and the J-W eGFR equation (n=5274 patients). Each orange circle represents an individual patient and independent measurement. Diagonal solid and broken orange lines represent the line of regression and its 95% confidence interval (95% CI). The best agreement appears to be between eGFR_{CKD-EPI} and eGFR_{MDRD}, eGFR measurements, with a small positive bias of 1.7 (95% CI, -18.6 to 21.9). For all equations, the agreement appears to be best at lower values with discrepancies increasing at higher eGFR values (for instance >100 ml/min). The worst agreement appears to be between eGFR_{CKD-EPI} and CG eCrCl and their body surface area (BSA)-modified counterparts. eGFR_{CKD-EPI}, Chronic Kidney Disease Epidemiology Collaboration; CKD-EPI_{BSA}, CKD-EPI × (patient's BSA/1.73); eGFR_{MDRD}, Modification of Diet in Renal Disease; MDRD_{BSA}, MDRD × (patient's BSA/1.73); CG CrCl, Cockcroft-Gault creatinine clearance; J-W eGFR, Janowitz-Williams eGFR.
understand their strengths, nuances, and pitfalls in the treatment of AKI. EPI resulted in the lowest frequency of C-AKI compared with other equations.

Later in 1999, the eGFRMDRD was approved for use in 1978. Therefore, it made its way into dosing guidelines. It was developed from 249 White patients with CKD. In this large cohort of patients treated with cisplatin-based chemotherapy, we compared various equations for estimating kidney function before cisplatin chemotherapy as they relate to subsequent C-AKI. Among various tested equations across a threshold of 60 ml/min, patients classified using the eGFRCKD-EPI had the highest PPVs and the AUC for C-AKI (Table 3). In addition, compared with other equations, use of a threshold of ≥60 ml/min per 1.73 m² by CKD-EPI resulted in the lowest frequency of C-AKI compared with other equations.

To compare the various equations, it is important to understand their strengths, nuances, and pitfalls in the context of cisplatin’s discovery and use in clinical practice. CG CrCl was the only equation available when cisplatin was approved for use in 1978. Therefore, it made its way into the pharmacokinetic studies of cisplatin and subsequently into dosing guidelines. It was developed from 249 White patients with CKD. Later in 1999, the eGFRMDRD was developed from 1628 Black and White men and women with CKD, and was shown to be more accurate than CG CrCl (17). By contrast, eGFRCKD-EPI was developed in 2009 from 12,150 patients of diverse backgrounds with and without CKD; it was the first equation to include normal subjects (10). This larger and more representative sample enabled eGFRCKD-EPI to generate an accurate and precise estimate of GFR compared with MDRD (6), particularly in those with a GFR ≥60 ml/min per 1.73 m² (18,19). Most patients receiving cisplatin have an eGFR ≥60 ml/min per 1.73 m², thus making eGFRCKD-EPI the most suitable equation for this population, and this is further supported by our data (Tables 2 and 3). Although the difference between estimates of GFR calculated by various equations is small (range of mean difference 2–14, Figure 1), these could still prove to be clinically significant, at least for some patients at the cusp, if a fixed cutoff (such as 50 or 60 ml/min) is used by an oncologist to determine which patients should receive cisplatin.

In 2007, another major development in the methods for measuring kidney function was the adoption of isotope dilution mass spectrometry (IDMS), which helped improve the reproducibility and accuracy of creatinine measurements (20). IDMS creatinine calibration was incorporated into the development of eGFRCKD-EPI and was retrospectively applied to the eGFRMDRD (21). This standardization was not possible for CG CrCl or the J-W eGFR. This lack of standardization and inability to modify CG CrCl by BSA are limitations of this method, especially in patients with cancer (17).

Overall cancer survival has increased to 67% (22), largely credited to treatments with a tolerable toxicity profile that have preserved tumor eradication properties (23). Cisplatin has led to a survival of over 95% in patients with testicular cancer (23). This success, however, has led to patients living longer, with the long-term treatment-related toxicity, at times leading to premature death. AKI resulting from nephrotoxicity and CKD (24) can contribute to premature cardiovascular mortality (25). In addition, patients with CKD have limited options for chemotherapy and are often left out of clinical trials (26). Hence, preserving kidney function for

### Table 4. Coefficient of variation and concordance correlation coefficient between various equations (n=5274)

<table>
<thead>
<tr>
<th>Equations</th>
<th>Coefficient of Variation, % (95% Confidence Interval)</th>
<th>Concordance Correlation Coefficient (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFRCKD-EPI and eGFRMDRD</td>
<td>7 (7 to 7)</td>
<td>0.88 (0.87 to 0.88)</td>
</tr>
<tr>
<td>eGFRCKD-EPI and CG eCrCl</td>
<td>19 (19 to 20)</td>
<td>0.55 (0.53 to 0.56)</td>
</tr>
<tr>
<td>eGFRMDRD and CG eCrCl</td>
<td>22 (21 to 22)</td>
<td>0.84 (0.82 to 0.85)</td>
</tr>
<tr>
<td>CKD-EPIBSA and MDRD_BSA</td>
<td>7 (7 to 7)</td>
<td>0.90 (0.90 to 0.91)</td>
</tr>
<tr>
<td>eGFRCKD-EPI and MDRD_BSA</td>
<td>12 (11 to 12)</td>
<td>0.75 (0.74 to 0.76)</td>
</tr>
<tr>
<td>eGFRMDRD and MDRD_BSA</td>
<td>10 (10 to 10)</td>
<td>0.85 (0.84 to 0.85)</td>
</tr>
<tr>
<td>eGFRMDRD and J-W eGFR</td>
<td>13 (13 to 13)</td>
<td>0.69 (0.67 to 0.70)</td>
</tr>
<tr>
<td>eGFRMDRD and J-W eGFR</td>
<td>15 (15 to 15)</td>
<td>0.59 (0.58 to 0.61)</td>
</tr>
<tr>
<td>CG eCrCl and J-W eGFR</td>
<td>11 (10 to 11)</td>
<td>0.80 (0.80 to 0.81)</td>
</tr>
</tbody>
</table>

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CKD-EPIBSA, CKD-EPI × (patient’s body surface area [BSA]/1.73); MDRD, Modification of Diet in Renal Disease; MDRD_BSA, MDRD × (patient’s BSA/1.73); CG CrCl, Cockcroft-Gault creatinine clearance; CG CrClBSA, CG CrCl × (patient’s BSA/1.73); J-W eGFR, Janowitz-Williams eGFR.

*a Root mean square method.

### Sensitivity Analyses

We performed sensitivity analyses using alternate definitions of AKI (i.e., 50% and 100% increase in creatinine over baseline [Table Supplemental Tables 2A, 2B, 3A, and 3B]). Using the definition of a 50% increase in creatinine over baseline, 279 (5%) patients had C-AKI and using the definition of a 100% increase in creatinine over baseline, 78 (2%) patients had C-AKI. As expected, using these alternate definitions, the power to detect a difference between individual equations was limited. Interestingly, the proportion of patients with C-AKI in the higher-risk group was lower than in the lower-risk group when using the definition of 50% increase in creatinine. This was the opposite to what we have shown using the more conservative definition. Accordingly, the PPVs and the AUCs were lower. However, given the high NPVs, these definitions are useful to assess which patients are less likely to develop C-AKI. The high accuracy is largely driven by the high number of “true negatives” because fewer patients were deemed to have AKI with these definitions.

### Discussion

In this large cohort of patients treated with cisplatin-based chemotherapy, we compared various equations for estimating kidney function before cisplatin chemotherapy as they relate to subsequent C-AKI. Among various tested equations across a threshold of 60 ml/min, patients classified using the eGFRCKD-EPI had the highest PPVs and the AUC for C-AKI (Table 3). In addition, compared with other equations, use of a threshold of ≥60 ml/min per 1.73 m² by CKD-EPI resulted in the lowest frequency of C-AKI compared with other equations.

To compare the various equations, it is important to understand their strengths, nuances, and pitfalls in the context of cisplatin’s discovery and use in clinical practice. CG CrCl was the only equation available when cisplatin was approved for use in 1978. Therefore, it made its way into the pharmacokinetic studies of cisplatin and subsequently into dosing guidelines. It was developed from 249 White patients with CKD. Later in 1999, the eGFRMDRD was developed from 1628 Black and White men and women with CKD, and was shown to be more accurate than CG CrCl (17). By contrast, eGFRCKD-EPI was developed in 2009 from 12,150 patients of diverse backgrounds with and without CKD; it was the first equation to include normal subjects (10). This larger and more representative sample enabled eGFRCKD-EPI to generate an accurate and precise estimate of GFR compared with MDRD (6), particularly in those with a GFR ≥60 ml/min per 1.73 m² (18,19). Most patients receiving cisplatin have an eGFR ≥60 ml/min per 1.73 m², thus making eGFRCKD-EPI the most suitable equation for this population, and this is further supported by our data (Tables 2 and 3). Although the difference between estimates of GFR calculated by various equations is small (range of mean difference 2–14, Figure 1), these could still prove to be clinically significant, at least for some patients at the cusp, if a fixed cutoff (such as 50 or 60 ml/min) is used by an oncologist to determine which patients should receive cisplatin.

In 2007, another major development in the methods for measuring kidney function was the adoption of isotope dilution mass spectrometry (IDMS), which helped improve the reproducibility and accuracy of creatinine measurements (20). IDMS creatinine calibration was incorporated into the development of eGFRCKD-EPI and was retrospectively applied to the eGFRMDRD (21). This standardization was not possible for CG CrCl or the J-W eGFR. This lack of standardization and inability to modify CG CrCl by BSA are limitations of this method, especially in patients with cancer (17).

Overall cancer survival has increased to 67% (22), largely credited to treatments with a tolerable toxicity profile that have preserved tumor eradication properties (23). Cisplatin has led to a survival of over 95% in patients with testicular cancer (23). This success, however, has led to patients living longer, with the long-term treatment-related toxicity, at times leading to premature death. AKI resulting from nephrotoxicity and CKD (24) can contribute to premature cardiovascular mortality (25). In addition, patients with CKD have limited options for chemotherapy and are often left out of clinical trials (26). Hence, preserving kidney function for
as long as possible to tolerate multiple lines of chemotherapy is crucial. Kidney function before and after cisplatin exposure is a major determinant of the long-term circulating platinum level, which can be detected up to 20 years after treatment (27,28).

One of the strategies to prevent these late effects and premature mortality from cancer therapy might be to improve patient selection by identifying those at higher risk for specific toxicities (2). To this end, the use of a predictive model for C-AKI that looks at baseline risk factors (2), along with an accurate estimate of kidney function to guide this decision, is critical, rather than an assessment of the baseline kidney function alone. This is further demonstrated by our finding of low AUCs in our models, containing only baseline kidney function estimates, regardless of the equation used (Table 3).

A few different groups have previously attempted to identify the most suitable equation to guide eligibility for platinum chemotherapy. Some studies have compared measured GFR with the various estimating equations. Janowitz et al. compared eGFR generated by various equations and compared it with $\text{Cr}^{51}$-EDTA clearance among 2582 White patients with cancer who received carboplatin. They concluded the eGFR$_{\text{CKD-EPI}}$ equation modified to the patient’s own BSA is the most accurate. Additionally, they proposed a new equation (J-W eGFR) that surpassed performance of eGFR$_{\text{CKD-EPI}}$. The major drawbacks to their equation included absence of a variable for race, a small and homogenous validation sample, creatinine assay not being traceable to IDMS, and lack of information on performance of this equation in patients with low eGFRs (5,29). Lindberg et al. (30) compared various glomerular filtration–estimating equations with $\text{Cr}^{51}$-EDTA clearance in 94 patients with head and neck cancer, and concluded that CG CrCl is superior to other methods. However, their study design allowed for up to 21 days between corresponding (matched) sCr and $\text{Cr}^{51}$-EDTA measurements that introduced the potential for inaccuracy. In addition, they used creatinine measurements from different cycles of chemotherapy as opposed to comparing a single baseline measurement by various equations as in our study. Given the marked differences in study design, it is unclear if their results can be compared with ours. Their results also differed from those by Funakoshi et al. (31), who compared the eGFR$_{\text{CKD-EPI}}$ and CG eCrCl equations in 50 patients with head and neck cancer using inulin clearance as the gold standard, and found 92% accuracy with eGFR$_{\text{CKD-EPI}}$ compared with 78% accuracy with the CG eCrCl equation.

Two groups compared the number of patients eligible to receive cisplatin using conventional cutoffs of 60 ml/min by CG CrCl and eGFR$_{\text{CKD-EPI}}$ and had conflicting results. Tsao et al. (32) retrospectively studied 116 patients with urothelial cancer and found that using eGFR$_{\text{CKD-EPI}}$ led to a 17% larger pool of eligible patients compared with CG. Pal et al. (33) retrospectively studied 126 patients with bladder cancer and, contrastingly, found that eGFR$_{\text{CKD-EPI}}$ classified a fewer number of patients eligible. We similarly compared the eligible patients in our cohorts and found a larger number of patients using eGFR$_{\text{CKD-EPI}}$ when compared with CG eCrCl or eGFR$_{\text{MDRD}}$ (94% versus 91% or 90% respectively). However, we believe the number of eligible patients lacks relevance as a standalone measure. Therefore, we went one step further by including data on C-AKI rates within groups of eligible and ineligible patients. We found that eGFR$_{\text{CKD-EPI}}$ had the lowest rate of C-AKI, despite classifying the highest number of patients as eligible (absolute difference of C-AKI between eligible and ineligible patients was 7%, $P<0.0001$).

The eGFR-estimating equations by design are indexed to a BSA of 1.73 m$^2$. Although this indexing has helped improve their accuracy over the CG equation for estimating GFR, it can still be suboptimal for patients with BSAs that differ widely from 1.73 m$^2$ (34). Therefore, we adjusted the eGFR to the patients’ own BSAs. However, our results were mixed, and the BSA-adjusted equations did not substantially outperform eGFR$_{\text{CKD-EPI}}$ for predicting C-AKI. Others have reported similar results recently (35).

Eligibility for cisplatin-based chemotherapy depends on several factors including, but not limited to, baseline kidney function, functional status, type of cancer, and availability of other treatment options. Such factors help a clinician determine the risk compared with benefit of cisplatin-based therapy for an individual patient. As an example, an oncologist may choose to offer cisplatin-based therapy for palliative intent to a patient with an eGFR of 40 ml/min per 1.73 m$^2$ who has no other treatment options, whereas they may choose to prescribe a less nephotoxic option for a young patient with an eGFR of 70 ml/min per 1.73 m$^2$ who has multiple treatment options. We have intentionally avoided being prescriptive about avoidance of cisplatin below a certain eGFR cutoff. However, in our experience, oncologists often use a CrCl of 60 ml/min or eGFR of 60 ml/min per 1.73 m$^2$ (or less often 50 ml/min per 1.73 m$^2$) as a general guideline for medical decision making on prescription and dose adjustment. Thus, we have presented data on the risk of C-AKI above and below this threshold using various equations.

Overall, on the basis of the results of our study and those of others, eGFR$_{\text{CKD-EPI}}$ is the most accurate equation, and it identifies patients at highest risk of C-AKI compared with other equations. However, the relative proportions of C-AKI across various equations were not profoundly different for two possible reasons: first, baseline kidney function by eGFR or eCrCl alone has not been consistently shown to predict C-AKI (25,36–40). Second, our cohort, despite being very large and inclusive, did not have many patients with very low eGFR (i.e., patients who would presumably be at highest risk of C-AKI). The mean eGFR$_{\text{CKD-EPI}}$ in the $<$60 ml/min per 1.73 m$^2$ group was 51.3 ml/min per 1.73 m$^2$. This suggests patients with very low eGFR who would have likely contributed to a greater difference in C-AKI between groups of eGFR or eCrCl are not routinely treated with cisplatin. Despite these findings, the contrast between the frequency of C-AKI among patients with eGFR $<$60 ml/min per 1.73 m$^2$ and among patients with eGFR $\geq$60 ml/min per 1.73 m$^2$ was the starkest when eGFR was calculated by CKD-EPI. However, it is important to note that given the overall low PPV and AUC values for C-AKI among all equations, the use of C-AKI as a standalone measure for weighing risks and benefits of treatment with cisplatin is insufficient. A clinical predictive model for C-AKI (2) and clinical judgement are other components to take into consideration.
Our study has several strengths. We studied a large cohort of patients with all types of cancer and a wide range of doses. Addition of C-AKI data offered a clinically relevant outcome for comparison. But our study does have some limitations. We did not have measured GFR to calculate accuracy. Our study population was mostly White, and these results need to be tested in more diverse populations. We did not collect data on the cancer type in our population, or on rates of recovery from C-AKI or development of CKD. Patients in our study had largely preserved eGFR, therefore potentially limiting our findings to patients with normal or mildly reduced eGFR. This study does not answer the question about the optimal equation for assessing effectiveness of cisplatin.

In conclusion, the \( \text{eGFR}_{\text{CKD-EPI}} \) equation appears to be the most accurate and clinically relevant equation in patients receiving cisplatin. CG eCrCl does not seem to offer any advantages in this population and its use should be avoided.

**Disclosures**

A. Partridge reports receiving royalties as an author from UpToDate and received travel support from Novartis during the conduct of the study. G. Curhan reports receiving personal fees from AstraZeneca, Dicerna, OM1, Orphan, Merck, RenalGuard, and Shire/Takeda; receiving grants from Shoebay Audiology outside the submitted work; receiving grants and personal fees from Decibel Therapeutics, and royalties from UpToDate. S. Motwani reports having a salaried position as a Deputy Editor at UpToDate (Wolters Kluwer). S. Waikar reports receiving personal fees from Cerus, CVS, GlaxoSmithKline, Harvard Clinical Research Institute, Janssen, Mass Medical International, Stratata, Takeda, VenBio, and Wolters Kluwer; receiving grants and personal fees from Allena; and has served as an expert witness for litigation related to cisplatin nephrotoxicity, Granuflo, mercury exposure, Omnican, and statins, all unrelated to this study. T. Choueiri reports holding a patent; reports research (institutional and personal) with Analysis Group, Alexion, AstraZeneca, Bayer, Bristol Myers-Squibb/ER Squibb and sons LLC, Calithera, Cerulean, Corvus, Eisai, Exelixis, Foundation Medicine Inc., F. Hoffmann-La Roche, Genentech, GlaxoSmithKline, Lilly, Merck, Novartis, Peloton, Pfizer, Prometheus Labs, Roche, Roche Products, Sanofi/Aventis, Takeda, and Tracon; reports receiving honoraria from American Society of Medical Oncology, AstraZeneca, Alexion, Sanofi/Aventis, Bayer, Bristol Myers-Squibb/ER Squibb and sons LLC, Cerulean, Clinical Care Options, Corvus, Eisai, EMD Serono, Exelixis, F. Hoffmann-La Roche, Foundation Medicine Inc., Genentech, GlaxoSmithKline, Harbor-side Press, Heron Therapeutics, Ipsen, Kidney Cancer Journal, L-path, Lancet Oncology, Lilly Oncology, Michael J. Hennessy Associates, Inc (Healthcare Communications Company with several brands such as OnClive, PeerView and Physicians’ education resource), Merck, Navinata Healthcare, National comprehensive cancer network (NCCN) Analysis Group, Novartis, Peloton, Pfizer, Platform Q, Prometheus Labs, Roche, Roche Products, Research to Practice, New England Journal of Medicine, and Up-to-Date; reports a consulting or advisory role at Alexion, AstraZeneca, Bayer, Bristol Myers-Squibb/ER Squibb and sons LLC, Cerulean, Corvus, Eisai, EMD Serono, Exelixis, Foundation Medicine Inc., Genentech, GlaxoSmithKline, Heron Therapeutics, Ipsen, Lilly, Lilly Ventures Merck, NCCN Analysis Group, Novartis, Peloton, Pfizer, Pionyr, Prometheus Labs, Roche, Sanofi/Aventis, Tempest, and Up-to-Date; reports stock ownership with Pionyr and Tempest; reports other present or past leadership roles as Director of GU Oncology Division at DF and past President of medical Staff at DF, member of NCCN Kidney panel and the Genitourinary Steering Committee, past chairman of the Kidney Cancer Association Medical and Scientific Steering Committee, KidneyCan Advisory board, Kidney Cancer Research Summit cochair (2019-); reports patents, royalties or other intellectual properties through the International Patent Application No. PCT/US2018/12209, entitled “PBRM1 Biomarkers Predictive of Anti-Immune Checkpoint Response,” filed January 3, 2018, claiming priority to US Provisional Patent Application No. 62/445,094, filed January 11, 2017, International Patent Application No. PCT/US2018/058430, entitled “Biomarkers of Clinical Response and Benefit to Immune Checkpoint Inhibitor Therapy,” filed October 31, 2018, claiming priority to US Provisional Patent Application No. 62/581,175, filed November 3, 2017; reports travel, accommodations, expenses, in relation to consulting, advisory roles, or honoraria as medical writing and editorial assistance support may have been funded by communications companies funded by pharmaceutical companies (ClinicalThinking, Envision Pharma Group, Fishawack Group of Companies, Health Interactions, Par- exel, Oxford PharmaGenesis); the institution (DFCI) may have received additional independent funding of drug companies or/and royalties potentially involved in research around the subject matter; CV provided upon request for scope of clinical practice and research; mentored several non-US citizens on research projects with potential funding (in part) from non-US sources/Foreign Components. Asmar Wood is a private company based in Beirut, Lebanon that provided a total of $100,000 in salary support to S. Alaiwi from July 1, 2018 to July 1, 2020 during her postdoctoral research fellowship at DFCI. Fondation Arc Pour La Recherche Sur Le Cancer is a not-for-profit foundation based in Villejuif, France that provided €256,014/mo in salary support to R. Flippot during his clinical training at DFCI from May 2, 2018 to November 2018. All remaining authors have nothing to disclose.

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**Author Contributions**

A.H. Partridge was responsible for the project administration, resources, supervision, and writing review and editing. G.C. Curhan was responsible for the conceptualization, investigation, methodology, project administration, resources, supervision, visualization, writing original draft, writing review and editing. J. Hu was responsible for the formal analysis and software. M.D. Kaymakalan was responsible for the methodology, resources, validation, and writing review and editing. S.S. Motwani was responsible for the conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, visualization, writing the original draft, and writing review and editing. S.S. Waikar was responsible for the conceptualization, methodology, writing the original draft, and writing review and editing. T.K. Choueiri was responsible for the conceptualization, resources, supervision, and writing review and editing.

**Supplemental Material**

This article contains supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000572020/-/DCSupplemental.

Supplemental Table 1. Median cisplatin dose by AKI status and by estimated glomerular filtration rate or estimated creatinine clearance (< or ≧ 60 ml/min).
Supplemental Table 2A. C-AKI frequency by classification of patients into values of <60 (‘higher risk’) or \( \geq 60 \) mL/min (‘lower risk’) using specified equations to estimate renal function (n=5274). C-AKI is defined by a 50% increase in creatinine over baseline.

Supplemental Table 2B. C-AKI frequency by classification of patients into values of <60 (‘higher risk’) or \( \geq 60 \) mL/min (‘lower risk’) using specified equations to estimate renal function (n=5274). C-AKI is defined by a 100% increase in creatinine over baseline.

Supplemental Table 3A. Area under the curve (AUC) for various equations with C-AKI as the classifier where C-AKI is defined as a 50% increase in creatinine over baseline.

Supplemental Table 3B. Area under the curve (AUC) for various equations with C-AKI as the classifier where C-AKI is defined as a 100% increase in creatinine over baseline.

References


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