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 cancer patients. Glomerular filtration rate (GFR) estimating 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), estimated GFR (eGFR) by Modification of Diet in Renal Disease (eGFRMDRD), Chronic Kidney Disease Epidemiology Collaboration (eGFRCKD-EPI) or 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 cancer patients treated with cisplatin-based chemotherapy at two large cancer centers. We ascertained the frequency of cisplatin-associated acute kidney injury (C-AKI) defined as a ≥0.3mg/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 positive predictive value (PPV), negative predictive value (PPV), accuracy, and area under the curve (AUC).

Results: Patients were predominantly middle-aged (58, IQR 49-66 years), overweight (BMI 26.2, IQR 23.1-29.8 kg/m²), and white (87.6%) with a median baseline creatinine of 0.8 mg/dl and median cisplatin dose of 99 mg. C-AKI developed in 11.5% of the cohort. eGFRCKD-EPI had the highest PPV as well as AUC. eGFRCKD-EPI and eGFRMDRD along with their BSA-modified counterparts had the closest agreement with the lowest CV (7.2, 95% CI 7.0-7.3) and the highest concordance. C-AKI was lowest when using eGFRCKD-EPI to define eGFR ≥60ml/min/1.73 m².

Conclusion: Based on 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 now 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 assessment of kidney function. Different methods including serum creatinine (sCr), estimation of creatinine clearance (eCrCl) by the Cockcroft-Gault (CG) equation, and glomerular filtration rate (eGFR) estimating equations by either the Modification of Diet in Renal Disease (eGFR\(_{MDRD}\)) or Chronic Kidney Disease Epidemiology Collaboration (eGFR\(_{CKD-EPI}\)) 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, GFR estimating equations, in addition to serum creatinine are the mainstay of evaluating kidney function in the clinical setting.

One reason for the relative popularity of eGFR\(_{CKD-EPI}\) equation amongst nephrologists is its higher accuracy at GFR \(\geq 60\text{ml/min/1.73m}^2\),\(^6,7\) a level above which most patients receiving cisplatin would fall. However, eGFR\(_{CKD-EPI}\) is still not widely utilized by oncologists for making treatment decisions.\(^4\) Barriers to adoption of eGFR\(_{CKD-EPI}\) are not entirely clear but may include absence of high quality evidence and the use of other formulae in the literature. Data are needed from cohorts with large enough 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 acute kidney injury (C-AKI) based on retrospectively applying various equations for estimating baseline kidney function among patients in this cohort.

METHODS

Study Population

We conducted an observational study of patients treated with cisplatin at Massachusetts General Hospital (MGH) or Dana-Farber/Brigham and Women’s Cancer center (DF/BWCC) 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 (RPDR) that collects data from all Partners-affiliated institutions including MGH and BWH, and 2) DFCI’s Oncology Data Retrieval System (OncDRS). The study was approved by the Institutional Review Board. This approval included a complete ethical review of data procurement, storage, and use.

We included patients 18 years of age or older treated with cisplatin who had at least one serum creatinine measurement within the month prior to 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 2.5 and above 97.5 percentile) because our goal was to compare various equations with each other, as 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 prior to 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 blood urea nitrogen and creatinine; and history of diabetes or hypertension recorded prior to index date using diagnosis codes.

Equations to estimate renal function

We calculated the eCrCl, eGFR, and body surface area (BSA) as well as BSA-modified estimates for all patients in the study using the following equations:

eCrCl by CG⁸:

$$CG\text{ eCrCl ml/min} = [(140\text{-age}) \times \text{weight} \times 0.85 \text{ if female}] / (SCr \times 72)$$

eGFR by MDRD⁹:

$$e\text{GFRMDRD (mL/min/1.73 m²)} = 175 \times (SCr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

eGFR by CKD-EPI¹⁰:

$$e\text{GFRCKD-EPI (mL/min/1.73 m²)} = 141 \times \min (SCr/\kappa, 1)^{\alpha} \times \max (SCr/\kappa, 1)^{1.209} \times 0.993^{\text{Age}} \times 1.018$$

where:

- $SCr$ is serum creatinine in mg/dL,
- $\kappa$ is 0.7 for females and 0.9 for males,
- $\alpha$ is -0.329 for females and -0.411 for males,
- min indicates the minimum of $SCr/\kappa$ or 1, and
- max indicates the maximum of $SCr/\kappa$ or 1

eGFR_J-W by Janowitz-Williams (J-W eGFR)⁵:

$$\sqrt{\hat{GFR}} = \beta_0 + \beta_1 \text{Age} + \beta_2 \text{BSA} + \beta_3 \ln(\text{Cre}) + \beta_4 \ln(\text{Cre})^2 + \beta_5 \ln(\text{Cre})^3 + (\beta_6 + \beta_7 \text{Age}) \{ \text{if Sex=M} \} + \beta_8 \text{Age x BSA} + \epsilon$$
Estimated BSA by Dubois and Dubois:\[^{11}\]:

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

W—weight (kg), H—height (cm)

BSA-based drug dosing is a common convention in Oncology practice today.\(^{12,13}\) We wanted to evaluate if modifying the estimate to the patient’s individual BSA has an impact on the association. At the time of derivation, \(e\text{GFR}_{\text{CKD-EPI}}\) and \(e\text{GFR}_{\text{MDRD}}\) were indexed to BSA,\(^{11}\) but CG \(e\text{CrCl}\) was not. \(e\text{GFR}\) estimating equations are indexed to a BSA of 1.73 \(m^2\) because that was the average BSA in young adults when indexing was first introduced.

Therefore, we performed the BSA modifications of \(e\text{GFR}\) equations as follows:

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

Where BSA stands for the individual patient’s BSA calculated as shown above

### Outcome

We defined C-AKI as a \(\geq 0.3\) mg/dl rise in serum creatinine 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 prior to index date was used as the baseline. Peak creatinine was defined as the highest creatinine value within 14 days after the index date.

### Statistical analysis

Continuous variables are presented as mean (standard deviation) or median (interquartile range), while categorical variables are described by frequency. Unadjusted associations between the covariates and the primary outcome were evaluated using \(\chi^2\) tests for categorical data, the t-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 plots were constructed for assessing agreement between various equations. We also calculated the coefficient of variation (CV) and concordance correlation coefficients. 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 using C-AKI as the outcome. 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 who had at least one baseline creatinine measurement in our system. For simplicity, all 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 (87.6%) with a median age of 58 years (IQR 49-66 years) and BMI of 26.2 kg/m² (IQR 23.1-29.8 kg/m²). Many had hypertension (37.8%), fewer had diabetes (12.5%), and median baseline creatinine was 0.8 mg/dl (IQR 0.7-1.0 mg/dl). The majority of patients (83.7%) 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 (IQR 60.1-143.5 mg). C-AKI developed in 606 of the 5274 patients (11.5%). PPV of C-AKI in patients with eGFR or eCrCl <60ml/min was overall low for all equations (12.5-18.0%) as a stand-alone measure for prediction of C-AKI. However, amongst the equations, it was the highest for eGFR_{CKD-EPI} and lowest for J-W eGFR. NPV for eGFR or eCrCl >60ml/min was high and nearly equal for all equations (88.6-89.0%) (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 area under the curve (AUC) for individual equations with C-AKI as the outcome and compared various equations by the DeLong test.\textsuperscript{16} The AUC for predicting C-AKI was significantly higher for eGFR_{CKD-EPI} (AUC 0.59, 95% CI 0.57-0.60, p<0.0001) compared with the other equations (Table 3).

**Comparison of Various Equations**

We constructed Bland-Altman (B-A) plots to examine the agreement between various equations as shown in Figure 1. The best agreement was between eGFR_{CKD-EPI} and eGFR_{MDRD} values with a small positive bias of 1.7 (95% CI -18.2, 21.6). The worst agreement was between MDRD and CG CrCl (bias -14.0, 95% CI -63.4, 35.4). For all equations, the B-A plots demonstrated that the agreement was best at lower kidney function values. To examine the disparity, the coefficient of variation (CV) and concordance correlation coefficient (CC) were calculated and yielded similar results. The eGFR_{CKD-EPI} and eGFR_{MDRD} and their BSA-modified counterparts had the lowest
CV (7.2, 95% CI 7.0-7.3) 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 18.9 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 60ml/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. Based on this classification, the number of ‘lower risk’ patients were calculated to be the highest for J-W eGFR (95%), followed by CKD-EPI_{BSA} (94%), eGFR_{CKD-EPI} (92.2%), MDRD_{BSA} (92.2%), CG eCrCl (91.8%), and MDRD (90.2%). We further calculated C-AKI frequencies in each of these hypothetical ‘lower risk’ and ‘higher risk’ groups (Table 2). eGFR_{CKD-EPI} had significantly fewer patients with C-AKI in the ‘higher risk’ compared with the ‘lower risk’ group (10.9% vs 18.0%, p<0.0001) suggesting beneficial dichotomization; followed by MDRD (11.0% vs 16.2%, p=0.0006) and CKD-EPI_{BSA} (11.3% vs 15.3%, 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 (Supplementary Table 5). C-AKI frequency was no different between patients in the ‘lower risk’ vs ‘higher risk’ groups using MDRD<sub>BSA</sub>, CG CrCl, CG CrCl<sub>BSA</sub> and the J-W eGFR equations.

**Sensitivity Analyses**

We performed sensitivity analyses using alternate definitions of AKI [i.e., 50% and 100% increase in creatinine over baseline of AKI (Supplementary tables 2a, 2b, 3a, and 3b)]. Using the definition of a 50% increase in creatinine over baseline, 279 (5.3%) patients had C-AKI and using the definition of a 100% increase in creatinine over baseline, 78 (1.5%) 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 50% increase definition. This was the opposite direction compared with what we have shown using the more conservative definition. Accordingly, the positive predictive values and the AUCs were lower. However, given the high negative predictive values, 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 prior to treatment as it relates to subsequent C-AKI. Among various tested equations across a threshold of 60 ml/min, patients classified using the
eGFR\textsubscript{CKD-EPI} had the highest PPV and the AUC for C-AKI (table 3). In addition, compared with other equations, use of a threshold of ≥60 ml/min/1.73m\(^2\) by CKD-EPI resulted in the lowest frequency of C-AKI compared with other equations.

In order 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 eGFR\textsubscript{MDRD} was developed from 1,628 black and white men and women with CKD, and was shown to be more accurate than CG CrCl.\textsuperscript{17} By contrast, eGFR\textsubscript{CKD-EPI} was developed in 2009 from 12,150 patients of diverse backgrounds with and without CKD; first equation to include normal subjects.\textsuperscript{10} This larger and more representative sample enabled eGFR\textsubscript{CKD-EPI} to generate an accurate and precise estimate of GFR compared with MDRD,\textsuperscript{6} particularly in those with a GFR ≥60 ml/min/1.73m\(^2\).\textsuperscript{18,19} A majority of the patients receiving cisplatin have an eGFR ≥60 ml/min/1.73 m\(^2\), thus making eGFR\textsubscript{CKD-EPI} the most suitable equation for this population, and this is further supported by our data (Tables 2 and 3). Even though the difference between estimates of GFR calculated by various equations small (range of mean difference 2 to 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 or should not get 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.\textsuperscript{20} IDMS creatinine calibration was incorporated into the development of eGFR\textsubscript{CKD-EPI} and was retrospectively applied to the
This standardization was not possible for CG eCrCl or the J-W eGFR. This lack of standardization and inability to modify CG eCrCl by BSA are limitations of this method, especially in patients with cancer.

Overall cancer survival has increased to 67% largely credited to treatments with a tolerable toxicity profile which have preserved tumor eradication properties. Cisplatin has led to a survival of over 95% in patients with testicular cancer. 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 chronic kidney disease can contribute to premature cardiovascular mortality. In addition, patients with CKD have limited options for chemotherapy and are often left out of clinical trials. 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.

One of the strategies to prevent these late effects and premature mortality from to cancer therapy might be to improve patient selection by identifying patients at higher risk for specific toxicities. To this end, the use of a predictive model for C-AKI that looks at baseline risk factors 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 $^{51}$Cr-EDTA clearance amongst 2582 white patients with cancer who received carboplatin. They concluded that 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.\textsuperscript{5,29} Lindberg et al compared various glomerular filtration estimating equations with $^{51}$Cr-EDTA clearance in 94 head and neck cancer patients and concluded that CG CrCl is superior to other methods.\textsuperscript{30} However, their study design allowed for up to 21 days between corresponding (matched) serum creatinine and $^{51}$Cr-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 who compared the eGFR$_{\text{CKD-EPI}}$ and CG eCrCl equations in 50 head and neck cancer patients 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.\textsuperscript{31}

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 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.\textsuperscript{32} Pal et al retrospectively studied 126 patients with bladder cancer and, contrastingly, found that eGFR$_{\text{CKD-EPI}}$ classified a fewer number of patients eligible.\textsuperscript{33} We similarly compared the eligible patients in our cohorts and also
found a larger number of patients using eGFR\textsubscript{CKD-EPI}, when compared with CG eCrCl or eGFR\textsubscript{MDRD} (94\% vs 91.0\% or 90.2\% respectively). However, we believe the number of eligible patients lacks relevance as a stand-alone 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\textsubscript{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 7.1\%, p<0.0001).

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

Eligibility for cisplatin-based chemotherapy is dependent upon 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/1.73m\textsuperscript{2} who has no other treatment options, whereas they may choose to prescribe a less nephrotoxic option for a young patient with an eGFR of 70 ml/min/1.73m\textsuperscript{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/1.73m\textsuperscript{2} (or less often 50 ml/min/1.73m\textsuperscript{2}) as a general guideline for medical
decision-making regarding prescription and dose adjustment. Thus, we have presented data regarding risk of C-AKI above and below this threshold using various equations.

Overall, based on 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.$^{36-41}$ Second, our cohort, despite being very large and inclusive, did not have many patients with very low eGFR (ie, patients who would presumably be at highest risk of C-AKI). The mean eGFR$_{\text{CKD-EPI}}$ in the <60 ml/min/1.73 m$^2$ group was 51.3 ml/min/1.73 m$^2$. This suggests that 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 between less than or $\geq$ 60 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 stand-alone measure for weighing risks and benefits of treatment with cisplatin is insufficient. A clinical predictive model for C-AKI$^2$ as well as 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 eGFR\textsubscript{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**

S Motwani reports Salaried position as a Deputy Editor at UpToDate (Wolters Kluwer). T Choueiri reports a patent; Research (Institutional and personal): AstraZeneca, Alexion, Bayer, Bristol Myers-Squibb/ER Squibb and sons LLC, Cerulean, Eisai, Foundation Medicine Inc., Exelixis, Ipsen, Tracon, Genentech, Roche, Roche Products Limited, F. Hoffmann-La Roche, GlaxoSmithKline, Lilly, Merck, Novartis, Peloton, Pfizer, Prometheus Labs, Corvus, Calithera, Analysis Group, Sanofi/Aventis, Takeda; Honoraria: AstraZeneca, Alexion, Sanofi/Aventis, Bayer, Bristol Myers-Squibb/ER Squibb and sons LLC, Cerulean, Eisai, Foundation Medicine Inc., Exelixis, Genentech, Roche, Roche Products Limited, F. Hoffmann-La Roche, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, EMD Serono, Prometheus Labs, Corvus, Ipsen, Up-to-Date, NCCN, Analysis Group, NCCN, Michael J. Hennessy (MJH) Associates, Inc (Healthcare Communications Company with several brands such as OnClive, PeerView and PER), Research to Practice, L-path, Kidney Cancer Journal, Clinical Care Options, Platform Q, Navinata Healthcare, Harborside Press, American Society of Medical Oncology, NEJM, Lancet Oncology, Heron Therapeutics, Lilly Oncology; Consulting or Advisory Role: AstraZeneca, Alexion, Sanofi/Aventis, Bayer, Bristol Myers-Squibb/ER Squibb and sons LLC, Cerulean, Eisai, Foundation Medicine Inc., Exelixis, Genentech, Heron Therapeutics, Lilly, Roche, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, EMD Serono, Prometheus Labs, Corvus, Ipsen, Up-to-Date, NCCN, Analysis Group, Pionyr, Tempest, Lilly Ventures; No speaker's bureau; Stock ownership: Pionyr, Tempest; No leadership or employment in for-profit companies; Other present or past leadership roles: Director of GU Oncology Division at Dana-Farber and past President of medical Staff at Dana-Farber), member of NCCN Kidney panel and the GU Steering Committee, past chairman of the Kidney Cancer Association Medical and Scientific Steering Committee), KidneyCan Advisory board, Kidney cancer Research Summit co-chair (2019-); Patents, royalties or other intellectual properties: -International Patent Application No. PCT/US2018/12209, entitled "PBRM1 Biomarkers Predictive of Anti-Immune Checkpoint Response," filed January 3, 2018, claiming priority to U.S. 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 U.S. Provisional Patent Application No. 62/581,175, filed November 3, 2017; Travel, accommodations, expenses,
in relation to consulting, advisory roles, or honoraria; 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, Parexel, Oxford PharmaGenesis, and others); The institution (Dana-Farber Cancer Institute) 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 S.A.L. is a private company based in Beirut, Lebanon that will provide a total of $100,000 in salary support to Dr. Sarah Abou Alaiwi from 7/1/2018 to 7/1/2020 during her post-doctoral research fellowship at DFCI. -Fondation Arc Pour La Recherche Sur Le Cancer is a not-for-profit foundation based in Villejuif, France that provides 2561.04€ per month in salary support to Dr. Ronan Flippot during his clinical training at DFCI from 5/2/2018 to 11/4/2018. A Partridge reports other from UpToDate and other from Novartis during the conduct of the study. S. S. Waikar reports receiving personal fees from Cerus, CVS, GlaxoSmithKline, Harvard Clinical Research Institute, Janssen, Mass Medical International, Strataca, Takeda, Venbio, Wolters Kluwer, grants and personal fees from Allena, and has served as an expert witness for litigation related to cisplatin nephrotoxicity, Granuflo, mercury exposure, Omniscan, and statins, all unrelated to the current study. G Curhan reports personal fees from RenalGuard, grants from Shoebox Audiometry, personal fees from AstraZeneca, personal fees from Shire/Takeda, grants and personal fees from Decibel Therapeutics, personal fees from OM1, other from UpToDate, personal fees from Dicerna, personal fees from Orfan, and personal fees from Merck outside the submitted work. All remaining authors have nothing to disclose.

**Funding**

None

**Author contributions**

S.S. Motwani: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing - original draft, Writing - review and editing.

T.K. Choueiri: Conceptualization, Resources, Supervision, Writing - review and editing.

A.H. Partridge: Project administration, Resources, Supervision, Writing - review and editing.

J. Hu: Formal analysis, Software.

M.D. Kaymakcalan: Methodology, Resources, Validation, Writing - review and editing.

Sushrut S. Waikar: Conceptualization, Methodology, Writing - original draft, Writing - review and editing.

Gary C. Curhan: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing - original draft, Writing - review and editing.
References:


doi:10.1371/journal.pone.0192124


Table 1: Clinical characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=5274)</th>
<th>C-AKI (n=606; 11.5%)</th>
<th>No C-AKI (n=4668)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, in years</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>87.6</td>
<td>90.1</td>
<td>87.3</td>
</tr>
<tr>
<td>Black (%)</td>
<td>3.0</td>
<td>3.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Others (%)</td>
<td>9.4</td>
<td>6.4</td>
<td>9.7</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>37.9</td>
<td>51.8</td>
<td>36.0</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>12.5</td>
<td>18.7</td>
<td>11.7</td>
</tr>
<tr>
<td>Baseline creatinine, mg/dl</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</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</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>Weight, kg</td>
<td>76.2 (64.1-88.5)</td>
<td>81.0 (68.1, 93.5)</td>
<td>75.5 (63.6, 87.7)</td>
</tr>
<tr>
<td>BMI, kg/m²</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</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</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>
</tbody>
</table>

Measures of eGFR and eCrCl

<table>
<thead>
<tr>
<th></th>
<th>eGFR&lt;sub&gt;CKD-EPI&lt;/sub&gt;, ml/min/1.73 m²</th>
<th>eGFR&lt;sub&gt;MDRD&lt;/sub&gt;, ml/min</th>
<th>MDRD&lt;sub&gt;BSA&lt;/sub&gt;, ml/min</th>
<th>CG eCrCl, ml/min</th>
<th>J-W eGFR, ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>91 (77-102)</td>
<td>86.4 (70.9, 98.5)</td>
<td>91.9 (77.4, 102.1)</td>
<td>90.4 (76.7, 107.0)</td>
<td>92.2 (79.3, 106.7)</td>
</tr>
<tr>
<td></td>
<td>97 (81-112)</td>
<td>81.5 (67.6, 100.4)</td>
<td>85.5 (72.4, 100.4)</td>
<td>90.2 (72.4, 111.7)</td>
<td>92.5 (76.8, 110.2)</td>
</tr>
<tr>
<td></td>
<td>85 (72-100)</td>
<td>93.5 (71.5, 120.8)</td>
<td>98.4 (78.2, 122.4)</td>
<td>90.2 (72.4, 111.7)</td>
<td>92.5 (76.8, 110.2)</td>
</tr>
<tr>
<td></td>
<td>92 (76-110)</td>
<td>93.3 (75.9, 111.7)</td>
<td>97.0 (82.0, 112.1)</td>
<td>90.4 (76.7, 107.0)</td>
<td>92.2 (79.3, 106.7)</td>
</tr>
<tr>
<td></td>
<td>98 (78-122)</td>
<td>90.4 (76.7, 107.0)</td>
<td>92.2 (79.3, 106.7)</td>
<td>90.4 (76.7, 107.0)</td>
<td>92.2 (79.3, 106.7)</td>
</tr>
</tbody>
</table>

All continuous variables are median and interquartile range. Units: CKD-EPI, MDRD are expressed in ml/min/1.73 m², remaining equations are expressed in ml/min

**Abbreviations:** CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CKD-EPI<sub>BSA</sub>: CKD-EPI x (patient’s BSA/1.73); MDRD: Modification of Diet in Renal Disease; MDRD<sub>BSA</sub>=MDRD x (patient’s BSA/1.73); CG eCrCl: Cockcroft-Gault creatinine clearance; J-W eGFR: Janowitz-Williams eGFR
Table 2: C-AKI frequency by classification of patients into values of <60 (‘higher risk’) or ≥60 ml/min (‘lower risk’) using specified equations to estimate renal function (n=5274).

<table>
<thead>
<tr>
<th>Method</th>
<th>Patients classified as high risk (ie, number below 60 ml/min)</th>
<th>&lt;60 ml/min (‘higher risk’)</th>
<th>≥60 ml/min (‘lower risk’)</th>
<th>P value comparing risk groups</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR CKD-EPI*</td>
<td>412/5274 (7.8%)</td>
<td>74/412 (18.0%)</td>
<td>532/4862 (10.9%)</td>
<td>&lt;0.0001</td>
<td>18.0%</td>
<td>89.0%</td>
<td>83.5%</td>
</tr>
<tr>
<td>CKD-EPI BSA</td>
<td>321/5274 (6.1%)</td>
<td>49/321 (15.3%)</td>
<td>557/4953 (11.3%)</td>
<td>0.04</td>
<td>15.3%</td>
<td>88.7%</td>
<td>84.3%</td>
</tr>
<tr>
<td>eGFR MDRD*</td>
<td>518/5274 (9.8%)</td>
<td>84/518 (16.2%)</td>
<td>522/4756 (11.0%)</td>
<td>0.0006</td>
<td>16.2%</td>
<td>89.0%</td>
<td>81.9%</td>
</tr>
<tr>
<td>MDRD BSA</td>
<td>412/5274 (7.8%)</td>
<td>55/412 (13.4%)</td>
<td>551/4862 (11.3%)</td>
<td>0.23</td>
<td>13.4%</td>
<td>88.7%</td>
<td>82.8%</td>
</tr>
<tr>
<td>CG eCrCl</td>
<td>431/5274 (8.2%)</td>
<td>58/431 (13.5%)</td>
<td>548/4843 (11.3%)</td>
<td>0.18</td>
<td>13.5%</td>
<td>88.7%</td>
<td>82.5%</td>
</tr>
<tr>
<td>J-W eGFR</td>
<td>257/5274 (4.9%)</td>
<td>32/257 (12.5%)</td>
<td>574/5017 (11.4%)</td>
<td>0.62</td>
<td>12.5%</td>
<td>88.6%</td>
<td>84.9%</td>
</tr>
</tbody>
</table>

*CKD-EPI and MDRD equations are expressed in ml/min/1.73m², the other equations are in ml/min

**Abbreviations:** C-AKI: Cisplatin associated acute kidney injury; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CKD-EPI BSA: CKD-EPI x (patient’s BSA/1.73); MDRD: Modification of Diet in Renal Disease; MDRD BSA = MDRD x (patient’s BSA/1.73); CG eCrCl: Cockcroft-Gault creatinine clearance; J-W eGFR: Janowitz-Williams eGFR

PPV: Positive predictive value of C-AKI amongst those at ‘higher risk’. NPV: Negative predictive value of absence of C-AKI amongst patients at ‘lower risk’
Table 3: Area under the curve (AUC) for various equations with C-AKI as the classifier

<table>
<thead>
<tr>
<th>Equations</th>
<th>AUC</th>
<th>95% CI</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>

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.
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% CI) *</th>
<th>Concordance correlation coefficient (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR\text{CKD-EPI} and eGFR\text{MDRD}</td>
<td>7.2 (7.0 to 7.3)</td>
<td>0.88 (0.87 to 0.88)</td>
</tr>
<tr>
<td>eGFR\text{CKD-EPI} and CG eCrCl</td>
<td>19.3 (18.9 to 19.7)</td>
<td>0.55 (0.53 to 0.56)</td>
</tr>
<tr>
<td>eGFR\text{MDRD} and CG eCrCl</td>
<td>21.8 (21.4 to 22.3)</td>
<td>0.54 (0.52 to 0.55)</td>
</tr>
<tr>
<td>CKD-\text{EPI}\text{BSA} and MDRD\text{BSA}</td>
<td>7.2 (7.0 to 7.3)</td>
<td>0.90 (0.90 to 0.91)</td>
</tr>
<tr>
<td>eGFR\text{CKD-EPI} and MDRD\text{BSA}</td>
<td>11.6 (11.4 to 11.8)</td>
<td>0.75 (0.74 to 0.76)</td>
</tr>
<tr>
<td>eGFR\text{CKD-EPI} and \text{CKDepi}\text{BSA}</td>
<td>10.9 (10.6 to 11.1)</td>
<td>0.78 (0.77 to 0.79)</td>
</tr>
<tr>
<td>CKD-\text{EPI}\text{BSA} and \text{MDRD}\text{BSA}</td>
<td>13.6 (13.4 to 13.8)</td>
<td>0.68 (0.66 to 0.69)</td>
</tr>
<tr>
<td>eGFR\text{MDRD} and \text{MDRD}\text{BSA}</td>
<td>10.2 (10.1 to 10.4)</td>
<td>0.85 (0.84 to 0.85)</td>
</tr>
<tr>
<td>eGFR\text{CKD-EPI} and J-W eGFR</td>
<td>13.1 (12.8 to 13.4)</td>
<td>0.69 (0.67 to 0.70)</td>
</tr>
<tr>
<td>eGFR\text{MDRD} and J-W eGFR</td>
<td>14.8 (14.5 to 15.2)</td>
<td>0.59 (0.58 to 0.61)</td>
</tr>
<tr>
<td>CG eCrCl and J-W eGFR</td>
<td>10.6 (10.2 to 10.8)</td>
<td>0.80 (0.80 to 0.81)</td>
</tr>
</tbody>
</table>

*Root mean square method

**Abbreviations**: CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CKD-EPI\text{BSA}: CKD-EPI x (patient’s BSA/1.73); MDRD: Modification of Diet in Renal Disease; MDRD\text{BSA}=MDRD x (patient’s BSA/1.73); CG CrCl: Cockcroft-Gault creatinine clearance; CG CrCl\text{BSA}: CG CrCl x (patient’s BSA/1.73); J-W eGFR: Janowitz-Williams eGFR

**Figure 1 legend**: Bland Altman plots comparing agreement between eGFR\text{CKD-EPI}, eGFR\text{MDRD}, CG CrCl and their BSA modified counterparts as well as 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% CI. The best agreement appears to be between eGFR\text{CKD-EPI} and eGFR\text{MDRD} eGFR measurements with a small positive bias of 1.7 (95% CI -18.6, 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\text{CKD-EPI} and CG eCrCl and their BSA-modified counterparts.

**Abbreviations**: eGFR\text{CKD-EPI}: Chronic Kidney Disease Epidemiology Collaboration; CKD-EPI\text{BSA}: CKD-EPI x (patient’s BSA/1.73); eGFR\text{MDRD}: Modification of Diet in Renal Disease; MDRD\text{BSA}=MDRD x (patient’s BSA/1.73); CG CrCl: Cockcroft-Gault creatinine clearance; J-W eGFR: Janowitz-Williams eGFR
The X-axis shows the mean of the two values being compared, whereas the Y axis shows the difference between the calculated values.