A new model for estimating glomerular filtration rate in patients with cancer

Authors
Tobias Janowitz#*1,2, Edward H. Williams#*, Andrea Marshall3, Nicola Ainsworth4, Peter B. Thomas5, Stephen J. Sammut1, Scott Shepherd6, Jeff White7, Patrick B. Mark8, Andy Lynch1, Duncan Jodrell1,2, Simon Tavaré1, and Helena Earl2.

Affiliations
1Cancer Research UK Cambridge Institute, Li Ka Shing Centre, University of Cambridge, Cambridge, CB2 0RE, United Kingdom.
2Department of Oncology, University of Cambridge, NIHR Cambridge Biomedical Research Centre and Addenbrooke’s Hospital, Cambridge, CB2 0QQ, United Kingdom.
3Warwick Clinical Trials Unit, University of Warwick, Coventry, CV4 7AL, United Kingdom.
4Department of Oncology, Queen Elizabeth Hospital, King’s Lynn.
5Department of Ophthalmology, University of Cambridge, Addenbrooke’s Hospital, Cambridge, CB2 0QQ, United Kingdom.
6Royal Marsden Hospital.
7NHS Greater Glasgow and Clyde
8Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, G12 8TA, United Kingdom.

#These authors contributed equally to the work.

*Correspondence to: tj212@cam.ac.uk or edward.williams@cruk.cam.ac.uk
Abstract

**Purpose** The glomerular filtration rate (GFR) is essential for carboplatin chemotherapy dosing, however, the best method to estimate GFR in patients with cancer is unknown. We identify the most accurate and least biased method.

**Methods** Data on age, sex, height, weight, serum creatinine, and results for GFR from $^{51}$Cr-EDTA excretion measurements ($^{51}$Cr-EDTA GFR) were obtained from Caucasian patients aged 18 years or older with histologically confirmed cancer diagnoses at the Cambridge University Hospital NHS Trust, UK.

We developed a new multivariable linear model for GFR using statistical regression analysis. $^{51}$Cr-EDTA GFR was compared to the estimated GFR (eGFR) from seven published models and our new model using an internal validation data set and root-mean-squared-error (RMSE) and median residuals. A comparison of carboplatin dosing accuracy based on an absolute percentage error more than 20% (APE > 20%) was undertaken.

**Results** Between August 2006 and January 2013 data from 2,471 patients were obtained. The new model improved the eGFR accuracy (RMSE 15.00ml/min (95% CI 14.12-16.00)) compared to all published models. Body surface area (BSA) adjusted CKD-EPI was the most accurate published models for eGFR (RMSE 16.30ml/min (95% CI 15.34-17.38)) for the internal validation set. Importantly, the new model reduced the fraction of patients with a carboplatin dose APE >20% to 14.17% in contrast to 18.62% for BSA adjusted CKD-EPI and 25.51% for the Cockcroft-Gault model. The results were externally validated.
Conclusion In a large data set, from patients with cancer, a new model improves eGFR and carboplatin dose calculations, when compared to BSA adjusted CKD-EPI, the model we identified as the best published model for determination of eGFR in patients with cancer.
Introduction

The glomerular filtration rate (GFR), the fluid volume filtered from the capillaries of the renal glomeruli into the Bowman’s capsule per unit time, is used for calculations of carboplatin chemotherapy doses.\(^1\) A number of direct GFR measurements exist, such as the calculation based on clearance of chromium 51 EDTA (\(^{51}\)Cr-EDTA).\(^2\) These methods are costly and require time and expertise. As a substitute, models for GFR estimation have been developed based on readily available data, such as serum creatinine concentrations, age, and sex of the patient.\(^3\)–\(^11\)

These published models for GFR have been mainly developed for non-cancer patient populations that are frequently enriched for patients with chronic kidney disease. Their usefulness in patients with cancer has been examined using only small data sets and limitations have been documented.\(^12\)–\(^16\)

Uncertainties regarding GFR estimation for patients with cancer represent an area of clinical need. Carboplatin chemotherapy doses calculated using GFR\(^1\) are administered to patients with seminoma, lung, breast, and ovarian cancer, in both adjuvant and palliative settings, where accurate dosing is critical to outcome and toxicity.\(^17\)–\(^27\) In addition, GFR measurements guide clinicians with regard to cisplatin use, which is nephrotoxic\(^28,\ 29\) and considered with caution in patients with reduced renal function.\(^30\)–\(^32\) We use the largest published oncology data set to identify the most accurate published model as well as to develop a new model to estimate GFR.
Methods

Detailed methods and a comprehensive description of the new model development are provided in the supplement.

Study profile and data set

The study profile is displayed schematically in Figure 1. The full data set was compiled at the Cambridge University Hospital NHS Trust, UK, from Caucasian patients aged 18 years or older with histologically confirmed cancer diagnoses and a serum creatinine measurement within 30 days of the $^{51}$Cr-EDTA GFR measurement. The data set was randomly split at a ratio of 4:1 for model development and internal model validation. An external validation data set of 111 male patients with stage 1 seminoma was obtained from the Beatson West of Scotland Cancer Centre, Glasgow, UK. No patient-identifiable data were used. Anonymised data included age, sex, height, weight, serum creatinine, and results for the accurate GFR value from $^{51}$Cr-EDTA measurements ($^{51}$Cr-EDTA GFR). Body surface area (BSA) was calculated using the Du Bois equation. $^{33}$ Height, weight and $^{51}$Cr-EDTA GFR were measured on the same day.

Assessment of published models

We compared the $^{51}$Cr-EDTA GFR with the GFR calculated using the following five published models, with and without BSA adjustment: Martin, Wright, Mayo, Modification of Diet in Renal Disease (MDRD), and chronic kidney disease epidemiology (CKD-EPI). The Cockcroft and
Gault and Jelliffe models which estimate creatinine clearance, an approximation of GFR, were also assessed.\textsuperscript{3–10}

We used the Calvert equation\textsuperscript{1} to compare the accuracy of a carboplatin dose with an area under the curve (AUC) of 5 (mg/ml/min) (AUC5) calculated from \textsuperscript{51}Cr-EDTA GFR with eGFR for all models.

**Model generation**

In brief, we developed a linear model for the relationship between GFR and the predicting variables. The Box-Cox method\textsuperscript{34} gave a suitable transformation to approximate normality. The model variables were chosen using minimisation of a five-fold cross-validation, a leave-one-out cross validation, and the Bayesian information criterion (BIC) in a stepwise method starting from a model containing only an intercept term (null model).\textsuperscript{35–40} To address the random component associated with this selection process for the five-fold cross-validation criterion, 2000 repetitions of the process were performed and the most frequent model was taken forward.

**Laboratory methods and GFR calculation**

GFR was calculated from the measurement of \textsuperscript{51}Cr-EDTA in three plasma samples taken over time after intravenous injection of 2MBq of \textsuperscript{51}Cr-EDTA. Serum creatinine was measured using the kinetic Jaffe method.
Statistics

Median percentage error (PE), root-mean-squared error (RMSE), interquartile range (IQR) of the residuals, and median absolute percentage error (APE) were used to assess the accuracy of each GFR model for predicting measured $^{51}$Cr-EDTA GFR. A median APE of >20% was considered a clinically relevant deviation of the carboplatin dose. RMSE results are expressed with a 95% confidence interval (CI) calculated using the chi-squared distribution. All median statistics are reported with IQRs.
Results

Between August 2006 and January 2013 data from 2,471 patients were obtained. The data set was divided randomly into data from 1,997 patients (80%) for model development and from 494 patients (20%) for internal validation of the new model. Table 1 summarizes the patient characteristics that were similar between data sets. Serum creatinine and $^{51}$Cr-EDTA GFR were measured within 30 days (median 6 days, IQR 2-9 days). The median for $^{51}$Cr-EDTA GFR was 81ml/min (IQR 63-103ml/min) indicating that most patients had near normal kidney function. The external validation data set consisted of 111 patients with stage 1 seminoma, who had a median age of 39 years (IQR 33-46 years) and median $^{51}$Cr-EDTA GFR of 113ml/min, (IQR 101-131ml/min, Table 1).

We used the full data set to compare the performance of seven published candidate models and BSA adjusted models (Mayo, Jelliffe, MDRD, CKD-EPI). For estimating GFR, CKD-EPI is the most accurate model with the lowest RMSE at 21.17ml/min (95% CI 20.60-21.78). BSA adjustment improves accuracy for the CKD-EPI, MDRD and Jelliffe models. After BSA adjustment CKD-EPI has the lowest RMSE (16.63ml/min, 95% CI 16.18-17.10), is least biased (residual median of 0.54ml/min, IQR -10.18-9.16), and has a median PE closest to zero (-0.78%, IQR -14.09-11.19%), the smallest residual IQR (19.34ml/min), and the smallest median APE (12.33%, IQR 5.77-21.62%).
With regard to carboplatin doses, calculated by the Calvert equation (Dose [mg] = AUC [mg x min/ml] x (GFR [ml/min] + 25 [ml/min])),\(^1\) where dose is linearly related to GFR, the statistics of RMSE, residual median, and IQR of residuals, are direct reflections of the GFR results, but median PE and median APE are different. We determined the fraction of patients receiving doses with a clinically relevant APE of more than 20%, which is smallest for BSA adjusted CKD-EPI (17.38%). BSA adjusted CKD-EPI, therefore, is the best performing published model for estimation of GFR and calculation of carboplatin dose in our data set from patients with cancer (Supplemental Table 2).

Next, we investigated if our large data set could be used to develop a new and better model. We first noticed that the untransformed GFR data were not normally distributed (Supplemental Figure 1A and C). The Box-Cox method suggested that modelling the square root of GFR would satisfy the assumptions of a linear model (Supplemental Figure 1B and D). The relationship between square root GFR and untransformed creatinine was not linear (Supplemental Figure 2A and 3E). Of several tested data transformations natural logarithmic transformation achieved the best linearity between GFR and the transformed creatinine (Supplemental Figure 2D and 3F). However, graphical analysis of the residual against transformed serum creatinine concentration for a simple model (a model that has the variable ln(Cre), sex and BSA) showed that further transformations were required (Supplemental Figure 2E). Including a quadratic and cubic term further improved the linearity and better modelled the complex relationship (Supplemental Figure 3H), and significantly improved the model (p-value <0.0001, F-test). Age, body surface
area, height, and weight had an approximately linear relationship with square root GFR (Supplemental Figure 2B-C 3A-D).

For the model selection on the development dataset we used the leave-one-out, 5-fold and BIC criteria. All three of our criteria selected the same model (Equation 1). The 5-fold criterion selected the model 854 times out of the 2000 repetitions.

Using the internal validation data set, we compared the performance of the new model to the performance of the published models. Bland-Altman and residual plots indicated that the new model is more accurate, less biased, and less heteroscedastic, i.e. it has more constant variance in different sub-populations (Figure 2 and Supplemental Figure 4). These plots also demonstrate that the new model, CKD-EPI, and BSA adjusted CKD-EPI are least prone to overfitting. The new model is the most accurate and second least biased model for estimating GFR (Figure 3A and C, Supplemental Table 3). It has the lowest RMSE at 15.00ml/min (95% CI 14.12-16.00) and a median residual of 0.51ml/min (IQR -7.99-9.67). For the BSA adjusted CKD-EPI model the RMSE and the residual median are 16.30ml/min (95% CI 15.34-17.38) and -0.03ml/min (IQR -9.92-10.13), and for the Cockcroft-Gault model 23.75ml/min (95% CI 22.36-25.33) and -0.79ml/min (-14.93-9.54), respectively (Figure 3C).

We consider using the new model for calculation of carboplatin dosing for patients with cancer the most important area of potential clinical impact. Thus we investigated the fraction of patients who would have received an AUC5 carboplatin dose that deviated more than 20% from the
accurate dose using $^{51}$Cr-EDTA GFR. This fraction was smallest for the new model with an APE>20% of 14.17% in contrast to 18.62% for the BSA adjusted CKD-EPI and 25.51% for the Cockcroft-Gault model (Figure 3D and Supplemental Table 4).

We also investigated the utility of the new model to guide prescription of cisplatin, an important chemotherapeutic agent that causes nephrotoxicity. Of the 58 patients within the internal validation data set who had a measured GFR of less than 50ml/min, a value that warrants caution for full dose cisplatin administration, the new model returned an eGFR below this value for 31 (53%) patients. This compares with 36 (62%) and 35 (60%) patients when the BSA adjusted CKD-EPI or the Cockcroft-Gault model were used, respectively. In turn, of the 436 patients that had a measured GFR of more than 50ml/min, a total of 9 (2.1%) (new model), 16 (3.7%) (BSA adjusted CKD-EPI), and 29 (6.7%) (Cockcroft-Gault) patients had an estimated GFR below 50ml/min.

This demonstrates limitations of point estimates. However, the new model satisfies all linear modelling assumption and thus predictive confidence intervals for future unobserved GFR values can be estimated (Figure 4). For 54 (93%) patients out of the 58 patients with a measured GFR of less than 50ml/min the 95% predictive confidence interval includes 50ml/min. This increased detection rate of “at risk” patients is offset by predictive confidence intervals that contain 50ml/min for 158 (36%) patients with a measured GFR above 50ml/min.
To assess the model robustness, the variable selection process was repeated for the three criteria on 100 different random partitions of the full data set into development and validation data sets. The new model remained most frequently returned and has the form

Equation 1: \[ \sqrt{\text{GFR}} = \beta_0 + \beta_1 \text{Age} + \beta_2 \text{BSA} + \beta_3 \ln(\text{Cre}) + \beta_4 \ln(\text{Cre})^2 + \beta_5 \ln(\text{Cre})^3 \]

\[ + (\beta_6 + \beta_8 \text{Age}) \{\text{if Sex = M}\} + \beta_0 \text{Age} \times \text{BSA} + \varepsilon \]

where the errors \( \varepsilon \) are independent, mean zero normally distributed random variables with a constant variance \( \sigma^2 \). The final coefficients \( \beta_0, \ldots, \beta_8 \) were determined by fitting the model using the full data set so as to get the most accurate values (Table 2).

Diagnostic plots for the new model confirmed that no single data point was influential in the full data set (highest Cook’s distance value: 0.094) (Supplemental Figure 5A and B). Importantly there was still no heteroscedasticity in the final linear model and we thus confirm that calculation of confidence intervals (prediction intervals) for the estimated GFR values is appropriate (Supplemental Figure 5C and D).

Finally, we externally validated the model using a dataset from a different cancer centre. GFR estimation (Supplemental Table 3, Figure 3B) and dose accuracy assessment for carboplatin
demonstrated that the new model remained the most accurate compared to all other models. The RMSE for the GFR calculated with the new model was 18.94ml/min compared to 21.33ml/min for BSA adjusted CKD-EPI, and 32.32ml/min for Cockcroft-Gault (Figure 3B-C and Supplemental Table 5). The carboplatin AUC5 APE>20% was 11.71% for the new model and 18.92% for the BSA adjusted CKD-EPI, the next best model (Figure 3D and Supplemental Table 6). Of the 111 patients in the external validation data set 105 (94.6%) had the measured GFR within the 95% confidence interval (Supplemental Figure 6).
Discussion

Our work is based on the analysis of data from a total of 2582 patients with cancer and reports two potentially practice changing results. Firstly, we find that BSA adjusted CKD-EPI is the most accurate and least biased published model for estimation of GFR. Secondly, we develop a new model that improves the estimation of GFR further and allows calculation of predictive confidence intervals for this estimation. Both findings will help practicing oncologists who prescribe platinum based chemotherapy.

Determination of GFR is a cornerstone of the curative and palliative management of patients with carboplatin responsive cancer such as lung, ovary, triple negative and germline BRCA1/2 mutant positive breast cancer, and seminomas.\textsuperscript{18–27} Carboplatin doses are most commonly calculated using the Calvert equation,\textsuperscript{1} a linear relationship between GFR and dose. GFR measurements or estimates therefore directly influence dose accuracy. This is important because Carboplatin is dose-dependently linked to tumour response and toxicities.\textsuperscript{17} Methods to measure GFR after tracer injection\textsuperscript{2} are laborious and expensive and not considered routine clinical investigations. Consequently, oncologists often rely on methods to estimate GFR from biometric patient data and routine blood test results, most notably serum creatinine concentration. With the exception of the Wright equation\textsuperscript{8} that investigated 100 patients with cancer, these methods have been developed for purposes other than chemotherapy dosing and from data of non-cancer populations, which are enriched for patients with impaired kidney function compared to our data set.
Practice changing clinical trials of carboplatin chemotherapy have employed gold standard $^{51}$Cr-EDTA GFR measurements,$^{18–20}$ creatinine clearance using the Cockcroft-Gault model,$^{21–23}$ the Jelliffe model$^{24–27,42}$ or 24 hour urine creatinine collections.$^{19}$ This demonstrates absence of a consensus. The findings of our study show that out of the published methods unadjusted CKD-EPI predicts GFR and consequently carboplatin doses similarly well to the Jelliffe, Wright, and Cockcroft-Gault models in patients with cancer. We confirmed the finding of other studies that the inclusion of BSA in predictive models improves accuracy.$^{12}$ BSA adjusted CKD-EPI had the lowest RMSE and bias, as well as the smallest carboplatin dose APE >20% and should, therefore, be considered the best published creatinine based GFR estimation model.

Patients in the development group for the CKD-EPI model$^{10}$ were non-cancer patients and had a mean GFR of 68 ml/min/1.73m$^2$ and were thus different to the patient population in our study, the population of cancer patients who are scheduled to receive carboplatin or cisplatin chemotherapy. We hypothesised that we could derive a new model to predict GFR better for patients with cancer. We recognised that there are multiple approaches for developing a model for the relationship between the dependant variable, GFR, and the independent predicting variables. Square root transformed GFR is an approximately normally distributed variable, its relationship to the independent variables is approximately linear, and the resulting residuals have a mean of zero and constant variance. Therefore, we concluded that a linear model with this transformation of GFR was appropriate. Evidence from our internal and external validation work
suggests that our new model is the best currently available model to predict GFR in patients with cancer.

From a clinical point of view, the most important advantage of our new model is a reduction in the fraction of patients that receive a carboplatin dose that is more than 20% different from the dose calculated using $^{51}$Cr-EDTA GFR, even when compared to the BSA adjusted CKD-EPI model. The absolute reduction in the external validation set is from 34.23% for the Cockcroft-Gault and 18.92% for the BSA adjusted CKD-EPI model to 11.71% with the new model. In addition, we report the mean of the prediction as well as the variance and, therefore, the predictive confidence interval. This represents a further advantage, because it will provide clinicians with a gauge of the suitability to use the prediction in a given clinical context. For example, our analysis demonstrates that only 4 out of 58 patients from the validation data set with a measured GFR below 50ml/min did not contain this value in the 95% predictive confidence interval. We present the data for the value 50ml/min, but recognize that this value would be dependent on the clinical context.\textsuperscript{30–32} We acknowledge this fact by providing an estimated probability of the patient’s true GFR being below a user adjustable GFR value as part of an online tool to offer a clinical guide for prescription of cisplatin, a nephrotoxic chemotherapeutic.\textsuperscript{28, 29}

Further strengths of our study are the large data set from patients with cancer, the stringent methodology, and the internal and external validation of our findings. Our model is based on standard biometric data and can be easily used in clinical practice. The study is limited, however,
by the Caucasian only population, due to the single centre population demographics. Others have shown that adjustment factors improve GFR prediction for black patients\textsuperscript{6,10} and this should be a priority area for future investigations. The final coefficients reported in our study may be, to a degree, centre-dependent as a result of centre-dependent creatinine results, a problem that has been addressed by international guidelines to standardise creatinine reporting\textsuperscript{43} which are implemented at our centre. Using creatinine as the main explanatory variable in predicting GFR has its own limitations. Other predicting variables such as Cystatin C have been used, but were not available to us and their usefulness in patients with cancer is uncertain, because their levels may fluctuate in a cancer dependent and kidney function independent manner.\textsuperscript{44} We also did not analyse measurements of albumin, muscle mass, information on dietary and fluid intake, and co-morbidities such as diabetes mellitus.

Our findings may be relevant for a broad range of clinical decision making in patients with or without cancer diagnoses. GFR influences clinical management in the context of drug dose adjustments\textsuperscript{45} and decision making in the context of clinical organ support.\textsuperscript{41} Gold standard \textsuperscript{51}Cr-EDTA GFR measurement would usually not be performed in these contexts. Future research should also investigate if the new model can facilitate correlative and ultimately causative analysis of toxicity and dose accuracy relationships in clinical trials.
In summary, BSA adjusted CKD-EPI is the most accurate published model to predict GFR in patients with cancer. Our new model may present a new standard of care and should be investigated alongside BSA adjusted CKD-EPI in clinical practice.
Online tool

The following link provides access to an online tool that is built based on the new model:

https://sites.google.com/site/janowitzwilliamsgfr/

The tool provides for any given set of input data the eGFR according to the new model, an estimated predictive confidence interval for the true GFR (default setting at 95%), an estimated probability of the true GFR to be below or above an operator chosen value (default setting at 50ml/min), along with eGFR according to BSA adjusted CKD-EPI.
Author Contributions


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References


Figure titles and legends

Figure 1: Schematic representation of study workflow
Figure 2: Bland-Altman plots of estimated GFR and measured GFR for the new model and each of the published models. The average of measured GFR (mGFR) and estimated GFR (eGFR) was plotted against the difference of the two for the internal validation data set. Positive differences indicate underestimation and negative difference indicate overestimation. The plots are ordered in ascending order of RMSE of eGFR from top left to bottom right. The solid line on each plot represents the mean of the difference and the dashed line are drawn at the mean plus or minus 1.96 times the standard deviation of the difference. Points are coloured by sex, red = female, turquoise = male.
Figure 3: Graphical illustrations of statistics used to compare the new model and published models. (A-B) Boxplots of the residuals (measured GFR minus estimated GFR) for all published models and the new model using the internal validation data set (A) and the external validation data set (B) are shown. Notches delineate an approximate 95% confidence interval for the median residual, calculated as ±1.58*IQR/n⁰.⁵. A positive or negative value for the residual median indicates underestimation or overestimation bias respectively. (C) Graphical illustration of GFR RMSE in the internal and external validation data sets. Error bars describe the 95% confidence interval based on the Chi-squared distribution for the calculated RMSE. (D)
Graphical illustration of percentage of patients with a carboplatin dosing APE >20% in the internal and external validation datasets. For all plots: black = internal validation set; grey = external validation data set
Figure 4: Predictive confidence intervals for GFR of each patient in the internal validation data set. To obtain this figure the new model fitted on the development data set was applied to all patients in the internal validation data set. The measured GFR (red points) and the estimated GFR (black points) for each patient are illustrated. Each horizontal line represents a 95% predictive confidence interval for the patient, with patients ordered in accession by their estimated GFR. The vertical dashed line highlights the boundary at a GFR of 50ml/min below which cisplatin administration would be considered with caution by most clinicians. Out of the 494 patients in the internal validation data set, 24 (4.9%) have measured values outside their prediction interval.
Table 1. Patient characteristics

GFR = glomerular filtration rate

IQR = interquartile range

BSA = body surface area
Table 2. Final coefficients for new model

The table describes the coefficients ($\beta_i, i = 0, ..., 8$) of the final model (Equation 1) with the estimate value and standard deviation for each coefficient. The estimate for standard deviation of the residuals ($\sigma$) was 0.8417 to 4 significant figures.

* From t-test comparing coefficient value to 0

BSA = body surface area

Cre = blood serum creatinine

SexM = variable equals 1 if Sex is male, 0 otherwise

x1:x2 indicates interaction variable between variables x1 and x2