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New Model for Estimating Glomerular Filtration Rate in Patients With Cancer

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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
We obtained data on age, sex, height, weight, serum creatinine concentrations, and results for GFR from chromium-51 (^{51}Cr) EDTA excretion measurements (^{51}Cr-EDTA GFR) from white patients ≥ 18 years of age with histologically confirmed cancer diagnoses at the Cambridge University Hospital NHS Trust, United Kingdom. We developed a new multivariable linear model for GFR using statistical regression analysis. ^{51}Cr-EDTA GFR was compared with the estimated GFR (eGFR) from seven published models and our new model, using the statistics root-mean-squared-error (RMSE) and median residual and on an internal and external validation data set. We performed a comparison of carboplatin dosing accuracy on the basis of an absolute percentage error > 20%.

Results
Between August 2006 and January 2013, data from 2,471 patients were obtained. The new model improved the eGFR accuracy (RMSE, 15.00 mL/min; 95% CI, 14.12 to 16.00 mL/min) compared with all published models. Body surface area (BSA)–adjusted chronic kidney disease epidemiology (CKD-EPI) was the most accurate published model for eGFR (RMSE, 16.30 mL/min; 95% CI, 15.34 to 17.38 mL/min) for the internal validation set. Importantly, the new model reduced the fraction of patients with a carboplatin dose absolute percentage error > 20% to 14.17% in contrast to 18.62% for the BSA-adjusted CKD-EPI and 25.51% for the Cockcroft-Gault formula. The results were externally validated.

Conclusion
In a large data set from patients with cancer, BSA-adjusted CKD-EPI is the most accurate published model to predict GFR. The new model improves this estimation and may present a new standard of care.

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 on the basis of 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 on the basis of 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 noncancer 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

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both adjuvant and palliative settings, where accurate dosing is critical to both 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 used 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 development of the new model are provided in the Data 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, United Kingdom, from white patients ≥ 18 years of age with histologically confirmed cancer diagnoses and a serum creatinine measurement within 30 days of the ^{51}Cr-EDTA GFR–measurement (^{51}Cr-EDTA GFR). 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 male patients (n = 111) with stage I seminoma was obtained from the Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom. No patient-identifiable data were used. Anonymized data included age, sex, height, weight, serum creatinine concentration, and results for the accurate GFR value from ^{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 estimated 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-Gault and the Jelliffe models, which estimate creatinine clearance (ie, an approximation of GFR), were also assessed.[3-10]

We used the Calvert equation[1] to compare the accuracy of a carboplatin dose with an area under the curve (AUC) of 5 mg/mL/min (AUC5) calculated from ^{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[34] gave a suitable transformation to approximate normality. The model variables were

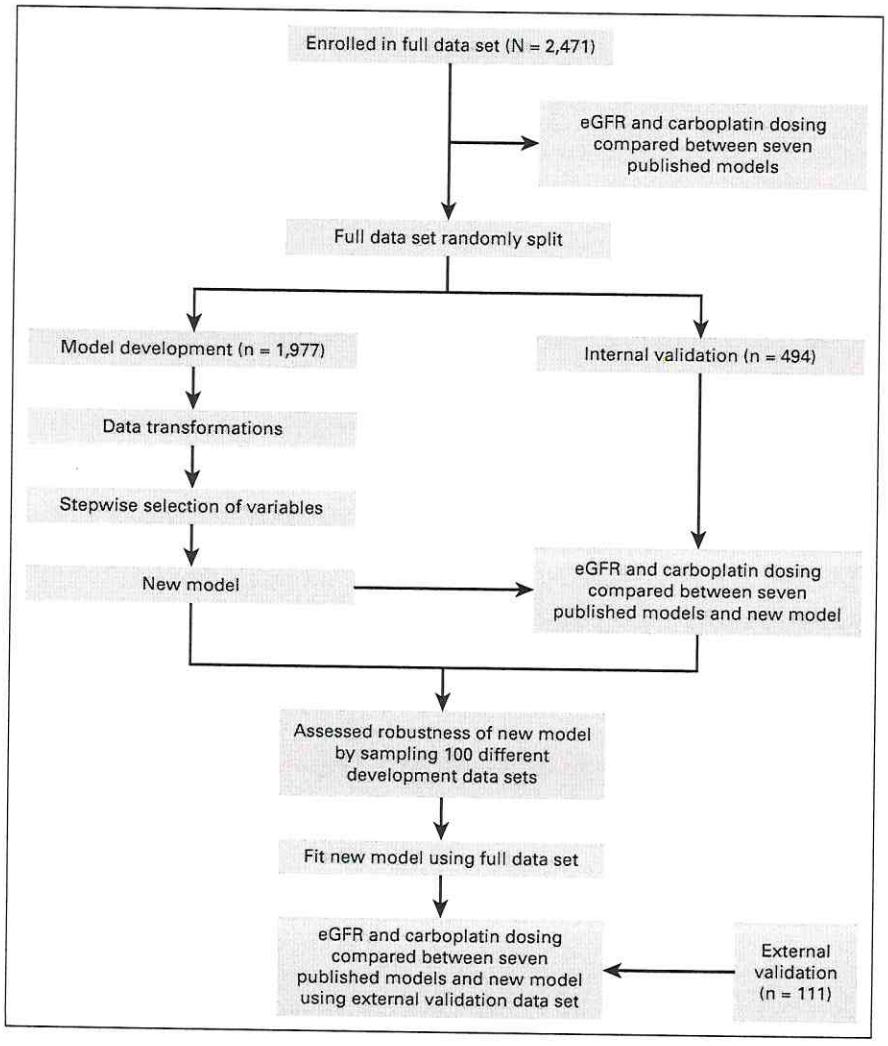

Fig 1. Schematic representation of study workflow. eGFR, estimated glomerular filtration rate.

chosen using minimization of a five-fold cross validation, a leave-one-out cross validation, and the Bayesian information criterion in a stepwise method starting from a model containing only an intercept term (null model).[35-40] To address the random component associated with this selection process for the five-fold cross-validation criterion, 2,000 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 ^{51}Cr-EDTA in three plasma samples taken over time after intravenous injection of 2 megabecquerel (MBq) of ^{51}Cr-EDTA. Serum creatinine (Cre) 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 > 20% was considered a clinically relevant deviation of the carboplatin dose. RMSE results are expressed with a 95% CI calculated using the χ^2 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 1,977 patients (80%) for model development and from 494 patients (20%) for internal validation of the new model. The patient characteristics were similar between the different data sets and are summarized in Table 1. Serum creatinine and ^{51}Cr-EDTA GFR were measured within 30 days (median, 6 days; IQR, 2 to 9 days). The median for ^{51}Cr-EDTA GFR was 81 mL/min (IQR, 63 to 103 mL/min), indicating that most patients had near-normal kidney function.[41] The external validation data set consisted of patients with stage I seminoma (n = 111), who had a median age of 39 years (IQR, 33 to 46 years) and a median ^{51}Cr-EDTA GFR of 113 mL/min (IQR, 101 to 131 mL/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, and CKD-EPI). For estimating GFR, CKD-EPI was the most accurate model, with the lowest RMSE at 21.17 mL/min (95% CI, 20.60 to 21.78 mL/min). BSA adjustment improved accuracy for the CKD-EPI, MDRD, and Jelliffe models. After BSA adjustment, CKD-EPI had the lowest RMSE (16.63 mL/min; 95% CI, 16.18 to 17.10 mL/min), was least biased (median residual, 0.54 mL/min; IQR, −10.18 to 9.16 mL/min), and had a median PE closest to zero (−0.78%; IQR, −14.09% to 11.19%), the smallest residual IQR (19.34 mL/min), and the smallest median APE (12.33%; IQR, 5.77% to 21.62%).

With regard to carboplatin doses, calculated by the Calvert equation: dose [mg] = Target AUC [mg/mL/min] × (GFR [mL/min] + 25 [mL/min]),[1] where dose is linearly related to GFR, the statistics of RMSE, median residual, 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 > 20%, which was smallest for BSA-adjusted CKD-EPI (17.38%). BSA-adjusted CKD-EPI, therefore, was the best-performing published model for estimation of GFR and calculation of carboplatin dose in our data set from patients with cancer (Data Supplement).

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 (Data Supplement). The Box-Cox method suggested that modeling the square root of GFR would satisfy the assumptions of a linear model (Data Supplement). The relationship between square root GFR and untransformed creatinine was not linear (Data Supplement). Of several tested data transformations, natural logarithmic transformation (ln) achieved the best linearity between GFR and the transformed creatinine (Data Supplement). However, graphical analysis of the residual against transformed serum creatinine concentration for a simple model (ie, a model that had the variables ln(Cre), sex, and BSA) showed that further transformations

Table 1. Patient Characteristics

Characteristic	Full Data Set	Development	Internal Validation	External Validation
No. of patients	2,471	1,977	494	111
Age, years*	61 (50-69), 18-92	61 (50-69), 18-92	63 (51-70), 18-89	39 (33-46), 21-69
Weight, kg*	73 (62-85), 37-163	74 (63-86), 37-149	73 (62-84), 42-163	86 (76-98), 51-161
Height, cm*	168 (161-176), 125-200	168 (161-176), 125-200	168 (160-175), 146-196	178 (174-182), 131-192
BSA, m^2*	1.84 (1.67-2.00), 1.24-2.79	1.84 (1.67-2.00), 1.24-2.67	1.83 (1.67-1.99), 1.31-2.79	2.04 (1.92-2.15), 1.48-2.73
Serum creatinine, mg/dL*	0.91 (0.77-1.07), 0.29-5.62	0.91 (0.77-1.07), 0.38-4.05	0.91 (0.77-1.08), 0.29-5.62	0.92 (0.81-1.01), 0.62-1.45
^{51}Cr-EDTA GFR, mL/min*	81 (63-103), 11-211	82 (64-103), 13-211	80 (62-103), 11-187	113 (101-131), 45-202
^{51}Cr-EDTA GFR subgroup†				
< 40 mL/min	117 (5)	86 (4)	31 (6)	0 (0)
40-60 mL/min	422 (17)	336 (17)	86 (17)	2 (2)
> 60 mL/min	1,932 (78)	1,555 (79)	377 (76)	109 (98)
Sex†				
Female	1,398 (57)	1,114 (56)	284 (57)	0 (0)
Male	1,073 (43)	863 (44)	210 (43)	111 (100)

Abbreviations: BSA, body surface area; ^{51}Cr, chromium-51; GFR, glomerular filtration rate; IQR, interquartile range.
*Data presented as median (IQR), range.
†Data presented as No. (%).