Multicentre validation of the CamGFR model for estimated glomerular filtration rate

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Abstract

Important oncological management decisions rely on kidney function assessed by serum creatinine-based estimated glomerular filtration rate (eGFR). However, no large-scale multicentre comparison of methods to determine eGFR in patients with cancer are available.

To compare the performance of formulas for eGFR based on routine clinical parameters and serum creatinine not calibrated with isotope dilution mass spectrometry (non-IDMS), we studied 3,620 patients with cancer and 166 without cancer who had their GFR measured with an exogenous nuclear tracer at one of seven clinical centres. The mean measured GFR was 86 ml/min. Accuracy of all models was centre-dependent, reflecting inter-centre variability of non-IDMS creatinine measurements. CamGFR was the most accurate model for eGFR (root-mean-squared-error (RMSE) 17.3 ml/min) followed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) model (RMSE 18.2 ml/min).

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Knowledge of kidney function measured as the glomerular filtration rate (GFR) informs clinical practice.1 GFR can be accurately measured (mGFR) using exogenous nuclear tracer clearance, but in practice is frequently estimated (eGFR) using models based on routine clinical and biochemical data, specifically serum creatinine concentration. Creatinine is commonly measured using Jaffe or enzymatic methods which in turn are calibrated using an isotope dilution mass spectrometry (IDMS) standard or a non-IDMS standard.2

Recently, we derived a new model for GFR (CamGFR) using data from patients with cancer treated at the Cambridge University Hospitals NHS Foundation Trust, United Kingdom.3 CamGFR modelled GFR on a square root scale using non-IDMS creatinine and biometric patient data and estimated GFR more accurately than other published models. This gain increased accuracy in GFR-based carboplatin chemotherapy dose calculations.3 Here we validate these findings for non-IDMS creatinine-based estimation of GFR using multicentre data from patients with and without cancer.

Data were from the University Hospitals NHS Foundation Trusts in Cambridge, Southampton4, and Manchester; Barts Health NHS Trust, London; a combined Welsh dataset5,6; Western General Hospital, Edinburgh; and the Peter MacCallum Cancer Institute, Melbourne7. Data on age, sex, height, weight, serum creatinine concentration, histopathologically confirmed cancer diagnosis, ethnicity, and mGFR were obtained. Either 51Cr-EDTA or 99mTc-DTPA clearance were used to measure GFR.8,9 Serum creatinine was determined by enzymatic or Jaffe methods within 30 days of the mGFR date (Table S1). Adult patients with creatinine levels between 0.20 mg/dL and 4.5 mg/dL were included. From patients with multiple mGFR values, we only included the first value by date. Body surface area (BSA) was calculated using the DuBois & DuBois equation.10 The study was conducted at each institution according to its relevant regulatory and ethical requirments.

We compared mGFR with eGFR provided by six published models (CamGFR3, Martin11, Wright12, Mayo13, Modification of Diet in Renal Disease (MDRD) version 18614, and CKD-EPI15), along with two models for creatinine clearance (Cockcroft-Gault16 and Jelliffe17).

To assessed model performance, statistics were determined for bias (residual median), precision (residual interquartile range (IQR)), and accuracy (root-mean-squared error (RMSE)) and clinical robustness, by calculating the proportion of patients with an absolute percentage error greater than 20% (1-P20) for eGFR. 95% confidence intervals (CI) and p-values were approximated using bootstrap resampling.18

Data from 3,786 patients were included; 3,484 patients had solid cancer, 136 had haematological cancer, and 166 had a non-cancer diagnosis (Table 1). Creatinine values and mGFR were obtained on the same day for 27% and within a week for 89% of patients (Figure S1). The median mGFR was 85 ml/min (IQR 61 to 109 ml/min). The median serum creatinine value was 0.95 mg/dL (IQR 0.83 to 1.11 mg/dL). The median age, height, weight and BSA were 60 years, 169 cm, 74 kg and 1.85 m2 respectively (Table 1). Centre-specific summary statistics are provided in the supplement (Figures S2-S4, Tables S2-S3).

CamGFR was significantly more accurate in estimating GFR than all other models, both by RMSE or 1-P20, followed by the CKD-EPI model (Figure 1, Figure S6, Table S5). The RMSE for the CamGFR model was 17.3 ml/min (CI 16.7 to 17.9 ml/min) and 18.2 ml/min (CI 17.6 to 18.7 ml/min) for the CKD-EPI model (p-value = 0.03) and the 1-P20 results for CamGFR was 0.295 (CI 0.280 to 0.309) and 0.318 (CI 0.303 to 0.333) for CKD-EPI, respectively (p-value = 0.03). In subgroup analyses CamGFR was the most accurate model for most patients subgroups divided by tumour type, age, BSA, serum creatinine, or sex (Figures S7-S10)

Finally, CamGFR had the lowest RMSE for both male and female patients and in six out of seven centres. Model performance was not consistent between centres (Table S5, Figure 1), probably reflecting differences in non-IDMS creatinine values (Figure S3).

We did not adjust the CamGFR model to include race as a potential variable for two reasons, the small number of black patients (n=22) and the absence of a statistically significant difference in BSA, mGFR, or serum creatinine when we compared 10 random data draws matched for age and sex between non-black and black patients (Figure S5, Table S4). Other studies have documented systematic differences for the relationship between eGFR and creatinine for black patients14,15 and our study is probably underpowered to detect this. The use of non-IDMS creatinine data in this study represents a further limitation.20 Differences between non-IDMS and IDMS creatinine exist2 and future work should expand the CamGFR model to IDMS-creatinine data use. Of note, the CKD-EPI model was developed for use with IDMS-creatinine measurements specifically, but still outperformed other models that have been developed with non-IDMS data.

The data were mostly from chemotherapy treatment naive patients with cancer and the longitudinal effect of treatment on eGFR requires further study. Probably attributable to the near-normal renal function of the majority of patients in our study, we find that the underlying diagnosis of the patients does not impact the suitability of the models significantly. CamGFR, developed on data from patients with cancer, performs best in non-cancer patients and CKD-EPI, developed on data from patients without cancer, performs well for data from patients with cancer.

This work is based on data from seven centres and confirms that of the available models the CamGFR model estimates GFR most accurately, but the CKD-EPI model performs nearly as well overall and across the spectrum of relevant subgroups. The greatest gain in accuracy by these newer models over the older models, such as Cockcroft-Gault and Wright, was observed in younger patients and patients with lower creatinine values, probably reflecting the differences in model development populations.  However, even considering the different patient populations in different centres, it is likely that errors in estimating GFR can be reduced by standardising the methods used to measure serum creatinine at different laboritories and use of appropriate models. Given the linear relationship between GFR and carboplatin dose via the Calvert equation21, improved estimates of GFR using CamGFR will translate into more accurate carboplatin prescriptions.

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Online tool

CamGFR is available online at <https://sites.google.com/site/janowitzwilliamsgfr/>

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| --- | --- | --- | --- | --- | --- | --- |
| Centre | Total | Solid cancer | Haematological cancer | Non-cancer | Female | Race - Black |
| Cambridge  | 404 | 227 | 114 | 63 | 198 | 6 |
| Edinburgh  | 597 | 472 | 22 | 103 | 245 | 0 |
| London-Barts | 108 | 108 | 0 | 0 | 0 | 0 |
| Manchester  | 1777 | 1777 | 0 | 0 | 1066 | 16 |
| Melbourne | 308 | 308 | 0 | 0 | 111 | 0 |
| Southampton | 436 | 436 | 0 | 0 | 0 | 0 |
| Wales | 156 | 156 | 0 | 0 | 89 | 0 |
| Total | 3786 | 3484 | 136 | 166 | 1709 | 22 |
|  |  |  |  |  |  |  |  |
|  | Mean | SD | Minimum | Q1 | Median  | Q3 | Maximum |
| GFR (ml/min)  | 86  | 32 | 9 | 61 | 85 | 109 | 209 |
| Creatinine (mg/dL) | 0.99 | 0.28 | 0.43 | 0.83 | 0.95 | 1.11 | 4.45 |
| Age (years)  | 57 | 16 | 18 | 45 | 60 | 70 | 91 |
| Weight (kg)  | 76 | 19 | 33 | 63 | 74 | 87 | 200 |
| Height (cm) | 169 | 11 | 137 | 160 | 169 | 177 | 204 |
| BSA (m2)  | 1.85 | 0.25 | 1.17 | 1.68 | 1.85 | 2.02 | 3.17 |

**Table 1**: Characteristics of study patients. Summary of categorical data split by centre (top). Summary of continuous data for all patients (bottom). GFR was measured using either 99mTc-DTPA (Edinbrugh and Melbourne) or 51Cr-EDTA (all others). GFR - Glomerular filtration rate, BSA - Body surface area (calculated using DuBois-DuBois), SD - Standard deviation , Q1 - 25th percentile, Q3 - 75th percentile

**Figure 1**: Performance analysis of commonly used and well performing models. Results for the five best-performing models (CamGFR, CKD-EPI, Wright, MDRD-186 and Cockcroft- Gault) for the 3,776 patients from the non-IDMS creatinine validation dataset are displayed. Performance analysis of the other models is included in Table S5. A pooled analysis of data from all centres and the individual centre analyses are shown. (first row) The residual (measured GFR - estimated GFR) median, which is a measure of a model’s bias, is displayed. (second row) The residual interquartile range (IQR), which is a measure of a model’s precision, is displayed. (third row) The root-mean-squared error (RMSE), which is a measure of a model’s accuracy, is displayed. Accuracy is a combination metric of bias and precision. (fourth row) The proportion of patients who have an absolute percentage error more than 20% (1-P20), which reflects clinical robustness by illustrating the proportion of patients with a clinically relevant error, is displayed.

The best results are closest to zero for the residual median, and the smallest value for IQR, RMSE, and 1-P20. All error bars are 95% confidence intervals calculated using bootstrap resampling with 2,000 repetitions and a normal distribution approximation.