

Subgroup and longitudinal analysis for estimation of Glomerular Filtration Rate in patients with cancer



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Background

Estimation of GFR is important for the management of patients with cancer and is often performed using serum creatinine measurements, which in turn are increasingly determined using isotope dilution mass spectrometry (IDMS) assays. Here we present in-depth validation for a new model (CamGFR) that we developed using pre-IDMS creatinine measurements. In addition, we examine the accuracy of different models for GFR in clinically relevant subgroups of patients, including those with high and low body mass index (BMI) and patients from different age groups.

Methods

Data on age, sex, height, weight, serum creatinine, and results for GFR from ^{51}Cr -EDTA excretion measurements (^{51}Cr -EDTA GFR) or technetium-99m-DTPA (99Te-DTPA) were obtained from 3268 patients with cancer who had non-IDMS creatinine measurements, were at least 18 years old, and had a histopathologically confirmed diagnosis of cancer. We obtained data from 5 UK centres along with 2 international centres. Using these data, we first validated the CamGFR model [1]. We compared it to all published models and report here the results for the best performing and most relevant previously published models CKD-EPI [2], MDRD 186, Wright and Cockcroft-Gault. We use estimators of three different metrics to examine the performance of all models. The residual (measured GFR - estimated GFR) median was used to assess bias, i.e. how far the value of the estimation is from the true value. The residual interquartile range (IQR) was used to assess precision, i.e. the variance of repeat estimations. Accuracy is a combination of these two metrics and was estimated using the root-mean-squared error (RMSE). We then examined the clinical relevance of the estimation. A carboplatin dose for AUC₅ was calculated using the Calvert equation. For all models, we determined the proportion of patients who would have received a dose with an error greater than 20% (1-P20) when eGFR was used. Confidence intervals for all statistics were calculated using bootstrap resampling with 2000 repetitions and the normal distribution approximation. We then examined accuracy of the different models in patient subgroups by creatinine, age and BMI. Lastly, we examined accuracy in repeat GFR measurement using longitudinal data for a small subset of 15 patients.

| | mean | sd | min | q25 | median | q75 | max |
|-----------------------|------|------|-------|------|--------|------|------|
| GFR (ml/min) | 86 | 31 | 9 | 62 | 84 | 107 | 211 |
| Creat (mg/dL) | 0.97 | 0.30 | 0.29 | 0.80 | 0.93 | 1.09 | 5.62 |
| Age (years) | 57 | 16 | 18 | 46 | 60 | 69 | 92 |
| Height (cm) | 169 | 11 | 94 | 161 | 168 | 176 | 204 |
| Weight (kg) | 76 | 19 | 33 | 63 | 74 | 86 | 200 |
| BSA (m ²) | 1.85 | 0.24 | 1.171 | 1.68 | 1.85 | 2.02 | 3.17 |

Table 1: Summary characteristics of non-IDMS creatinine validation data. GFR - Glomerular filtration rate, BSA - Body surface area (calculated using DuBois-DuBois). Total sample size of 5,539 patients including original Addenbrookes dataset.

References

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- Calvert BAH, Newell DR, Gumbrell LA, et al: Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 7:1748-1756, 1989

Results

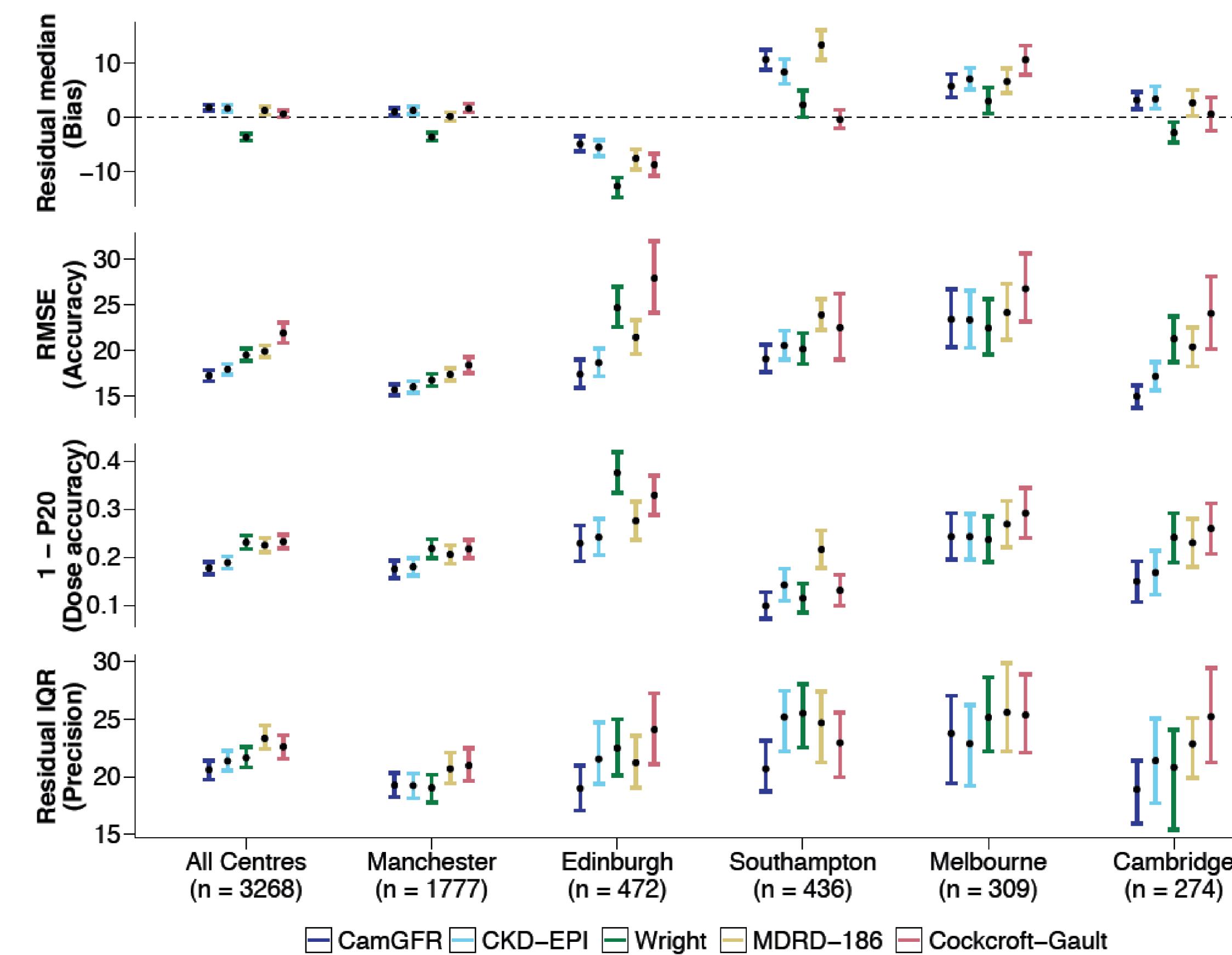


Figure 1: Performance of the CamGFR model and 4 commonly used models (CKD-EPI, Wright, MDRD-186 and Cockcroft-Gault) for the 3268 patients from the non-IDMS creatinine validation dataset. The performance is shown for all patients collectively and for each centre separately. The top plot shows the residual (measured GFR - estimated GFR) median which is a measure of a model's bias. The bottom plot shows the model root-mean-squared error (RMSE) which is a measure of a model's accuracy which itself is a combination of bias and precision. The third plot shows the proportion of patients who have a dose accuracy outside 20% of the gold standard (1 - P20), dose was calculated using the Calvert equation [3] with AUC = 5. All error bars are 95% confidence intervals calculated using bootstrap resampling with 2000 repetitions and a normal distribution approximation.

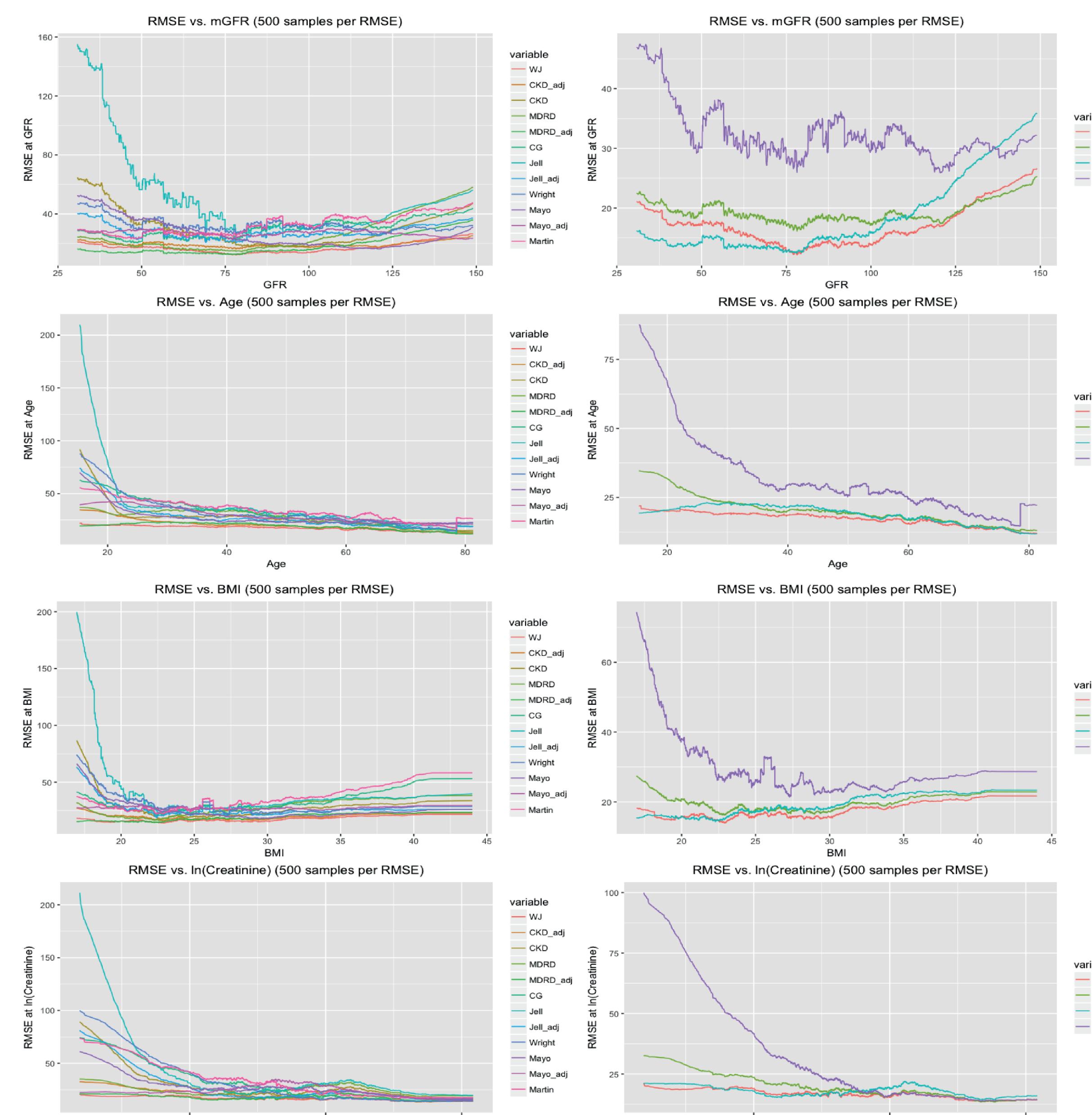


Figure 2: Performance of the pre-IDMS CamGFR model and all published models for the 3268 patients from the Non-IDMS creatinine data set. The performance is shown for all patients collectively from all centers with Non-IDMS data. RMSE for each plot is iteratively composed of 500 ordered samples, and the independent variables are presented as the mean of each 500-sample set. In sum, these charts show that the most accurate predictions are usually made in patients of a normal measured GFR, higher ln(creatinine) values, BMI between 25 and 30, and in older patients.

CamGFR is the most accurate model for GFR using all data and subsets of data from different centres. The lowest RMSE results in the most accurate dosing of carboplatin if estimated GFR is used. Subgroup analyses show that the most accurate predictions for GFR are made in patients of a normal range measured GFR, higher ln(creatinine) values, BMI between 25 and 30, and in older patients. In a small cohort from patients with sarcoma who required high dose chemotherapy over short periods of time, longitudinal GFR estimations were increasingly different from measured GFR.

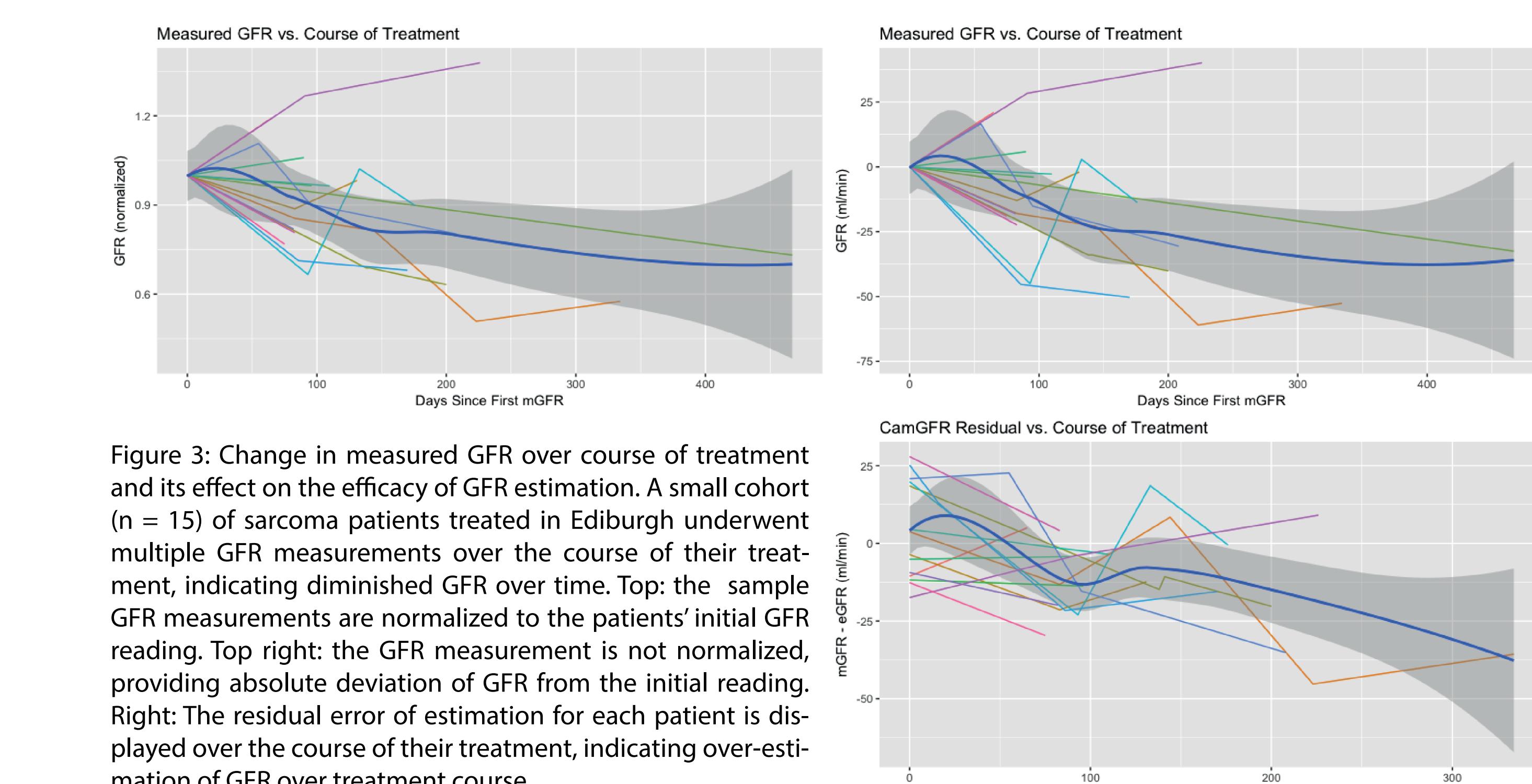


Figure 3: Change in measured GFR over course of treatment and its effect on the efficacy of GFR estimation. A small cohort (n = 15) of sarcoma patients treated in Edinburgh underwent multiple GFR measurements over the course of their treatment, indicating diminished GFR over time. Top: the sample GFR measurements are normalized to the patients' initial GFR reading. Top right: the GFR measurement is not normalized, providing absolute deviation of GFR from the initial reading. Right: the residual error of estimation for each patient is displayed over the course of their treatment, indicating over-estimation of GFR over treatment course.

Conclusions

This work has validated the CamGFR model for GFR estimation from Non-IDMS creatinine data in a large, multicentre cancer population. CamGFR is more accurate and less biased for Non-IDMS creatinine data than any other published model. This increased accuracy translates into more accurate carboplatin dosing when estimated GFR is used. Estimation of GFR is most accurate for older patients and patients with normal BMI. Preliminary work evaluating the utility of GFR estimation for repeat predictions in patients receiving anti-cancer treatment suggests that caution needs to be exercised when estimated GFR is used after high intensity chemotherapy.

Extended Findings

The CamGFR model has been extended and validated for use with IDMS data. Findings are similar when IDMS creatinine data are used for estimation of GFR.

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