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ORIGINAL RESEARCH

Glomerular filtration rate estimation for carboplatin dosing in patients with gynaecological cancers

A. Samani[1,2], R. Bennett[2†], K. Eremeishvili[3†], F. Kalofonou[2], S. Whear[1], A. Montes[3], R. Kristeleit[3], J. Krell[1,2], I. McNeish[1,2], S. Ghosh[3] & L. Tookman[1,2*]

[1]Department of Surgery and Cancer, Imperial College London, London; [2]Department of Medical Oncology, Imperial College Healthcare NHS Trust, London; [3]Guy's Cancer Centre, Guy's and St. Thomas' NHS Foundation Trust, London, UK

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Background: Carboplatin remains integral for treatment of gynaecological malignancies and dosing is based on glomerular filtration rate (GFR). Measurement via radiotracer decay [nuclear medicine GFR (nmGFR)] is ideal. However, this may be unavailable. Therefore GFR is often estimated using formulae that have not been validated in patients with cancer and/or specifically for gynaecological malignancies, leading to debate over optimal estimation. Suboptimal GFR estimation may affect efficacy or toxicity.

Methods: We surveyed several UK National Health Service Trusts to assess carboplatin dosing practise. We then explored single-centre accuracy, bias and precision of various formulae for GFR estimation, relative to nmGFR, before validating our findings in an external cohort.

Results: Across 18 Trusts, there was considerable heterogeneity in GFR estimation, including the formulae used [Cockcroft–Gault (CG) versus Wright], weight adjustment and area under the curve (AUC; 5 versus 6). We analysed 274 and 192 patients in two centres. Overall, CamGFR v2 (a novel formula for GFR estimation developed at Cambridge University Hospitals NHS Foundation Trust) excelled, showing the highest accuracy and precision. This translated into accuracy of hypothetical carboplatin dosing; nmGFR-derived carboplatin dose fell within 20% of the Cam GFR v2-derived dose in 86.5% and 87% of patients across the cohorts. Among the CG formula and its derivatives, using adjusted body weight in those with body mass index $\geq$25 kg/m^2 [CG-adjusted body weight (CG-AdBW)] was optimal. The Wright and unadjusted CG estimators performed most poorly.

Conclusions: When compared with nmGFR assessment, accuracy, bias and precision varied widely between GFR estimators, with the newly developed Cam GFR v2 and CG-AdBW performing best. In general, weight (or body surface area)-adjusted formulae excelled, while the unadjusted CG and Wright formulae or the use of AUC6 (versus nmGFR AUC5) produced risk of significant overdose. Thus, individual centres should validate their GFR estimation methods. In the absence of validation, CG-AdBW or CamGFR v2 is likely to perform well while unadjusted CG/Wright formulae or AUC6 dosing should be avoided.

Key words: gynaecological cancers, chemotherapy, carboplatin, glomerular filtration rate, toxicity

INTRODUCTION

Carboplatin-containing regimens remain first-line treatments for gynaecological cancers and are often used repeatedly. Carboplatin is almost exclusively excreted via glomerular filtration, with very little tubular secretion or reabsorption[1] allowing dosing based on glomerular filtration rate (GFR).[2,3] This enables predictable exposure to the drug as measured by the area under the curve (AUC) of the concentration versus time graph.

Predictable exposure minimises toxicity and optimises efficacy. One study, of 117 patients, showed a significant increase in treatment delays in those receiving a (higher) carboplatin dose calculated using GFR estimated from total body weight rather than adjusted or ideal body weight (AdBW or IBW).[4] Another study, of >1000 patients, showed correlation between dose and severity of thrombocytopenia/leukopenia. The study also showed significant improvements in objective response with increasing AUC up to 5-7 mg $\times$ min/ml.[5] Although not powered for statistical significance, a further study showed numerically higher rates of cycle delay and haematological toxicity in patients

*Correspondence to: Dr Laura Tookman, Department of Medical Oncology, Hammersmith Hospital, 72 Du Cane Road, London, W12 0HS, UK. Tel: +44 2033111234

E-mail: l.tookman@imperial.ac.uk (L. Tookman).

Twitter handles: @amit_samani1, @FKalofonou, @sharmisthaghosh

†Contributed equally.

with body mass index (BMI) >27 kg/m^2 when using actual body weight to dose carboplatin.[6]

A widely accepted gold-standard measurement of GFR, decay of the radiotracer ^{51}Cr-ethylenediaminetetraacetic acid (^{51}Cr-EDTA) (or similar), is labour intensive and may not be (immediately) available. In addition, it performs poorly in patients with ascites.[7] Therefore GFR is often estimated (eGFR) using one of several equations (Table 1). Only two have been validated in patients with cancer, the Wright formulae and the CamGFR v2 formula.[8,9]

Previously, eGFR for patients with gynaecological malignancies was commonly derived using the Jelliffe equation. Subsequently, many laboratories recalibrated their creatinine assays using an isotope dilution mass spectroscopy (IDMS)-traceable reference method. On average, this produces lower values than previous assays, raising concerns about potential carboplatin toxicity. This prompted the Gynecologic Oncology Group (GOG) to recommend estimation using the Cockcroft–Gault (CG) equation.[10] This equation may overestimate eGFR, especially in patients with a higher weight, so the GOG specifically recommended using AdBW for patients with a BMI ≥25 kg/m^2.[10]

Despite this, there remains wide variation and uncertainty in practice pertaining to GFR estimation. For this reason, we undertook a dual-centre study to validate the use of the AdBW-modified CG (CG-AdBW) equation and explore other formulae for estimating GFR in patients with gynaecological malignancies.

MATERIALS AND METHODS

Survey

To understand prescribing practice disparity in the UK, we undertook a survey of several National Health Service (NHS) Trusts (organisations). A list of Trusts was obtained online (https://www.nhs.uk/servicedirectories/pages/nhstrustlisting.aspx) and Trusts were numbered alphabetically. Numbers were chosen using a uniform random distribution (R, version 4.0.2; R Foundation, Vienna, Austria) and contact details for the relevant gynaecologic oncology unit sought. If no such unit existed, or details could not be found, the process was repeated until a total of 60 Trusts were selected. A survey (see Supplementary Appendix 1, available at https://doi.org/10.1016/j.esmoop.2022.100401) was emailed to consultant oncologists treating gynaecological cancers at each Trust. We received responses from 16 Trusts and combined data from Imperial College Healthcare NHS Trust and Guy's and St Thomas' NHS Foundation Trust for a total response rate of 29%.

Dataset and inclusion criteria

We initially performed a single-institution analysis of data from patients with gynaecological malignancies treated with carboplatin-containing regimens between 1 January 2015 and 10 July 2018 at Imperial College Healthcare NHS Trust, London (Imperial). Findings were compared with a cohort of patients treated between 1 January 2019 and

Table 1. Common formulae for GFR estimation

Name	Formula for female	Validation cohort	Comments
Cockcroft–Gault[11]	$CrCl = [(140 - age) \times wt] \times 0.85/(0.814 \times S_{cr})$	249 hospitalised male patients.	CrCl measured using 24-h urine collection and creatinine measured using the non-IDMS method.
(4 variable) Modification of Diet in Renal Disease (MDRD)[12]	$eGFR = 175 \times (S_{cr}/88.4)^{-1.154} \times age^{-0.203} \times 0.742 \times 1.212$ (if black)	1070 patients with renal disease aged ≤70 years and validated in a further 558 patients	GFR measured using ^{125}I-iothalamate. Does not require weight so result given per 1.73 m^2 BSA. Equation modified for IDMS. Assumes linearity of BSA versus GFR.
Jelliffe[13]	$CrCl = \{98 - [0.8 \times (age - 20)]\} \times 0.9/(S_{cr}/88.4)$	128 serial observations on 15 patients (6 female) in a renal transplant unit	CrCl was measured using 24-h urine collection and creatinine measured using the non-IDMS method.
Wright[8]	$eGFR = [6580 - (38.8 \times age)] \times BSA \times 0.832/S_{cr}$	Derived from 62 patients with cancer (24 with EOC) and validated in 38 more (12 with EOC)	Several versions including for both Jaffe and enzymatic creatinine assays.
Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[14]	$eGFR = 141 \times \min(S_{cr}/0.7, 1)^{-0.329} \times \max(S_{cr}/0.7, 1)^{-1.209} \times 0.993^{age} \times 1.018 \times 1.159$ (if black)	Derived from 5504 patients with renal disease and validated in a further 2750 patients internally + 3896 patients externally	GFR measured using ^{125}I-iothalamate. Creatinine measured using the IDMS method. Does not require weight so result given per 1.73 m^2 BSA. Few patients in studies were >70 years old and there was only minor variation in ethnicity.
CamGFR[15] and CamGFR v2[9]	See Supplementary Appendix 2 (Equations 2.10 and 2.11), available at https://doi.org/10.1016/j.esmoop.2022.100401	CamGFR: 3786 patients (3620 with cancer, 468 with gynaecological malignancy) CamGFR v2: 3083 IDMS creatinine measurements	CamGFR was validated using non-IDMS creatinine values, while CamGFR v2 resulted in separate formulae for non-IDMS and IDMS creatinine values. Numbers include development and validation cohorts.

For all formulae age is measured in years.

BSA, body surface area; CrCl, estimated creatinine clearance (ml/min); eGFR, estimated glomerular filtration rate (ml/min or ml/min/1.73 m^2; EOC, epithelial ovarian cancer; IDMS, isotope dilution mass spectroscopy; min/max, minimum or maximum value in parentheses respectively; S_{cr}, serum creatinine (mg/dl); wt, weight.

31 May 2020 at Guy's Cancer Centre, Guy's and St. Thomas' NHS Foundation Trust, London (Guy's).

Anonymised data from patients were included if the patients:

1) were aged ≥18 years and had received their first exposure to a carboplatin-containing regimen for a gynaecological malignancy, with dose calculated using the Calvert formula;
2) had a GFR measurement (nmGFR) calculated from plasma decay of ^{51}Cr-EDTA (Imperial) or Technetium-99m-diethylenetriaminepentaacetic acid (99mTc-DTPA; Guy's);
3) had weight and creatinine levels measured <28 days prior to acquisition of nmGFR.

The requirement for only a single weight and creatinine prior to nmGFR was based on real-world practice, where GFR is usually estimated using single creatinine and weight values. However, as a sensitivity analysis, we corroborated our finding on a subset of patients who had two values for both weight and creatinine, measured within 28 days of nmGFR, with both values concordant within 10%.

Data collection

Demographic data were collected in anonymised form from the Trusts' systemic anticancer therapy databases, including age, height, weight, primary tumour site, serum creatinine (S_{cr}), nmGFR and prescribed AUC for carboplatin.

At Imperial, S_{cr} was measured using the Jaffe (IDMS) method (ARCHITECT, Abbot Diagnostics, UK). nmGFR was calculated following injection of 3 MBq of ^{51}Cr-EDTA at 1.5 MBq/min with blood samples taken at 2 and 4 h after the injection dose. S_{cr} at Guy's was measured using a Roche IDMS-traceable assay. nmGFR was calculated following injection of 99mTc-DTPA using a three-blood-sample process in accordance with British Nuclear Medicine Society guidance.[16]

Study aims

The primary outcome/aim was to determine the agreement between nmGFR and CG-AdBW, and specifically to compare this with the agreement between nmGFR and unadjusted CG, IBW-adjusted CG (CG-IBW) or the novel CamGFR v2 (see below for methods used to assess agreement).

Secondary outcomes/aims were to determine the agreement between nmGFR and other equations for estimation, including The Modification of Diet in Renal Disease (MDRD), Jelliffe, Wright or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).

Formulae

Definitions of formulae for equations used to estimate GFR are presented in Supplementary Appendix 2, available at https://doi.org/10.1016/j.esmoop.2022.100401. Importantly, where CG formulae were adjusted for weight (CG-IBW or CG-AdBW), this was only applied to those patients with a BMI ≥25 kg/m^2. GFR for those with a BMI <25 kg/m^2 was always estimated using actual body weight. In addition, formulae that do not include weight as a parameter (e.g. Jelliffe, CKD-EPI) were assessed in both unmodified and modified [body surface area (BSA)-adjusted] form (Supplementary Appendix 2, available at https://doi.org/10.1016/j.esmoop.2022.100401).

Statistical analysis

Statistical analyses were carried out using R version 4.0.2.

Agreement was measured by three methods, described below.

First, association between eGFR and nmGFR was measured using Pearson's correlation and Lin's concordance correlation coefficient (CCC).[17] Perfect positive correlation along the line $y = x$ results in a CCC of 1, while any other correlation (including perfect Pearson correlation on a line other than $y = x$) would generate a CCC of <1. Regression coefficients were calculated using least squares linear regression.

Second, agreement was demonstrated graphically using Bland–Altman plots. These were constructed by plotting the difference between estimated and measured GFR against measured GFR (nmGFR). Means and limits of agreement (calculated as 1.96 × standard deviation) were represented along with regression lines fitted with least squares linear regression.

Finally, we measured accuracy, precision and bias in the following ways:

(i) Accuracy: This was defined by P_{30}, the proportion of eGFR measurements that lay within 30% of the corresponding nmGFR.
(ii) Bias: This was defined as the median percentage error (MPE), where percentage error for each patient is: [(calculated CrCl or GFR − measured GFR)/measured GFR] × 100
(iii) Precision: This was defined as the median absolute percentage error (MAPE), where absolute percentage error for each patient is: [(calculated CrCl or GFR − measured GFR)/measured GFR] × 100

As an exploratory analysis, we examined the percentage change in carboplatin dose following conversion from eGFR dosing to nmGFR dosing as follows:

eGFR dose: (eGFR + 25) × target AUC.
nmGFR dose: (nmGFR + 25) × target AUC.
Percentage change: [(eGFR dose − nmGFR dose)/eGFR dose] × 100.

Finally, we also looked at dose discrepancy between the use of AUC6 with eGFR and subsequent conversion to AUC5 with nmGFR. This is a practice adopted by some centres in our survey while also being recommended in some large clinical trials.[18,19]

RESULTS

Survey

We conducted a brief survey to investigate carboplatin dosing practices in UK hospitals. We combined data from 16

Trusts with results from Imperial and Guy's (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100401).

Although a small sample, there was considerable heterogeneity in the availability and indications for nmGFR acquisition. All but one Trust had access to nmGFR testing but only five performed nmGFR in all patients, indicating that many Trusts routinely rely on formulae to estimate GFR. Furthermore, there was heterogeneity in the methods used for estimating GFR in terms of the specific formulae used (CG versus Wright). Three Trusts used the Wright formula while the other 15 used CG. Moreover, even in those who used CG for estimation, there was heterogeneity in whether weight adjustment was used. Eight Trusts used CG with actual body weight in all patients while the remaining seven used modified body weight (adjusted or ideal) in at least some patients. Finally, no Trusts exclusively used AUC6 for dosing based on estimated GFR. However, four Trusts used AUC6 dosing in specific circumstances. This included if prescribing single-agent carboplatin or in patients with GFR <115 ml/min.

Baseline demographics

Of 305 patients treated with their first cycle of carboplatin at Imperial, 274 fulfilled the criteria for analysis. Of 202 patients treated at Guy's Hospital, 192 were eligible. Baseline demographics for both cohorts are shown in Table 2. The majority of patients in both cohorts had ovarian cancer although the percentage was higher at Imperial (64.8%) than at Guy's (52.1%). Age, BMI and S_{cr} were very similar in both cohorts, while nmGFR was higher for Guy's patients with a median of 76 ml/min versus 70 ml/min for the Imperial cohort.

There were 111 and 93 patients, respectively, in the Imperial and Guy's sensitivity cohorts (which only included patients with two values for weight and creatinine within 28 days of nmGFR, both concordant within 10%) with demographics similar to those shown above (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100401).

Table 2. Baseline demographics

	Imperial (n = 274)	Guy's (n = 192)
Age, years:		
Mean (95% confidence interval)	62.3 (60.4-64.2)	61.9 (60.3-63.6)
Median (range)	63 (19-90)	62 (21-86)
Diagnosis, n (%) (n = 128 for Imperial):		
Ovarian	83 (64.8)	100 (52.1)
Endometrial	32 (25.0)	67 (34.9)
Cervical	13 (10.2)	21 (10.9)
Vulval/vaginal	0 (0)	4 (2.1)
Body mass index:		
Mean (95% confidence interval)	27.4 (26.4-28.4)	26.7 (25.8-27.6)
Median (range)	26.0 (14.6-79.7)	25.8 (15.1-51.4)
Serum creatinine (μmol/l):		
Mean (95% confidence interval)	68.1 (65.9-70.3)	66.1 (64.6-69.6)
Median (range)	64.5 (42-154)	64.5 (34-202)
Measured glomerular filtration rate (ml/min):		
Mean (95% confidence interval)	71.2 (68.1-74.2)	75.1 (72.2-78.0)
Median (range)	70 (18-158)	76 (23-140)

Baseline demographics for both cohorts. Ovarian cancer includes fallopian tube and primary peritoneal carcinomas.

Correlation and regression

We next performed correlation and simple linear regression to assess the relationships between eGFR and nmGFR. This is illustrated for our primary formulae (unadjusted CG, CG-IBW, CG-AdBW, CamGFR v2; Figure 1) and all other formulae (Supplementary Figures S1 and S2, available at https://doi.org/10.1016/j.esmoop.2022.100401).

In both cohorts, least-squares regression lines (except for unmodified CG) had y-intercept values >0 and slope coefficients of <1 indicating a general tendency to underestimate GFR for each additional unit of nmGFR.

Among the CG formulae, this effect was most pronounced for CG-IBW with a slope coefficient of 0.72. Conversely, CG-AdBW had a modelled slope that was closest to 1 with coefficients of 0.9 and 0.92 in the Imperial and Guy's cohorts, respectively.

Of all 10 formulae tested, CG-AdBW and CamGFR v2 had the joint highest Lin's CCC (see the Methods section) in the Imperial cohort (0.79), while CamGFR v2 produced the highest CCC in the Guy's cohort (0.77). Across the two cohorts, the highest mean CCC resulted from estimation using CamGFR v2 (0.78) and CG-AdBW (0.76).

The results from the sensitivity analysis aligned with those from the overall cohort, with CG-AdBW and CamGFR v2 producing the highest mean CCC values (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2022.100401).

Bland–Altman plots

To aid in the visualisation of agreement, we constructed Bland–Altman plots using the various estimators of GFR versus nmGFR as a reference gold standard (Figure 2, Supplementary Figures S4 and S5, available at https://doi.org/10.1016/j.esmoop.2022.100401).

Overall, CamGFR v2 produced the lowest mean difference between nmGFR and estimated GFR (1.85 ml/min and −4.24 ml/min in the Imperial and Guy's cohorts, respectively). It also produced the tightest limits of agreement although there was a trend towards underestimation with increasing nmGFR values.

Among the remaining formulae, the CG-AdBW estimates had the lowest absolute mean differences between measured and estimated GFR, with consistent values between both cohorts (5.36 ml/min and 0.68 ml/min for the Imperial and Guy's cohorts, respectively). CG-IBW also demonstrated low mean differences (−2.46 ml/min and −6.48 ml/min, respectively). However, it demonstrated a stronger negative trend, tending to underestimate nmGFR at high GFRs. Conversely, the Wright formula produced the highest average difference between estimated and measured GFR of 21.86 ml/min and 17.83 ml/min at Imperial and Guy's, respectively.

These results were consistent in the sensitivity analysis with CamGFR v2 and CG-AdBW again producing the smallest

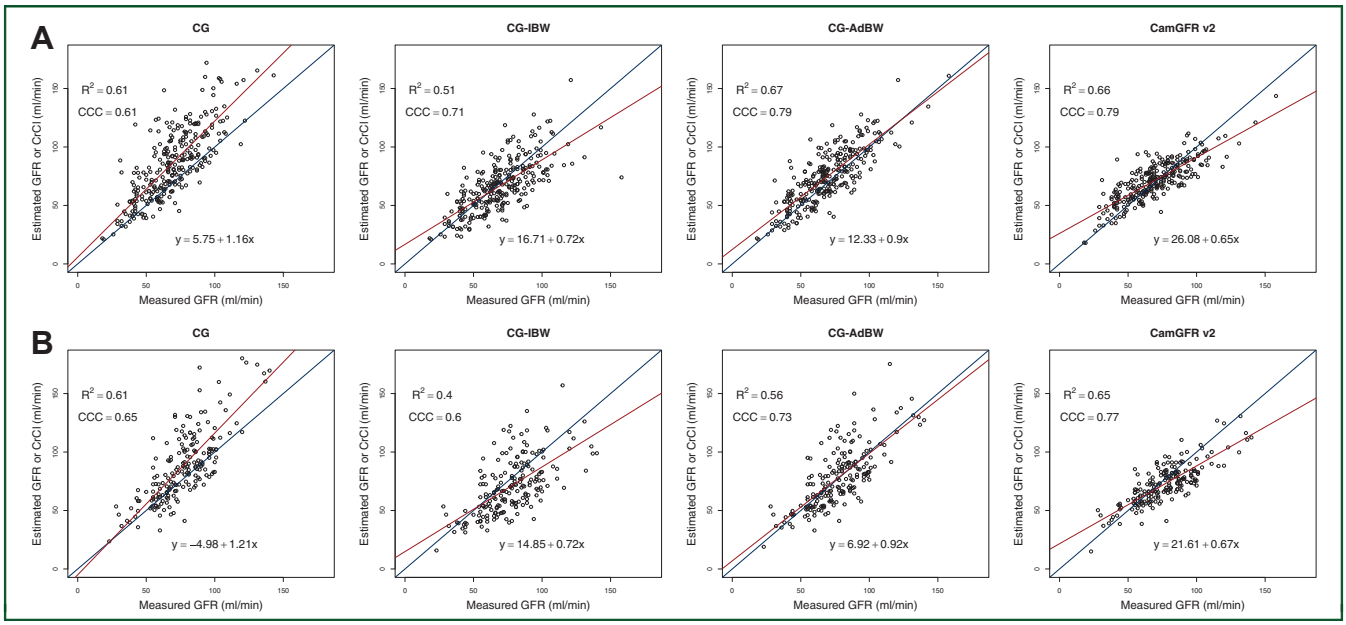

Figure 1. Pearson and Lin's correlation between measured and estimated glomerular filtration rate (GFR).
Relationship between given estimates of GFR and measured GFR for (A) Imperial cohort and (B) Guy's cohort. CG, Cockcroft—Gault, which was modified for IBW (ideal body weight) or AdBW (adjusted body weight); R^2, Pearson's coefficient of determination; CCC, Lin's concordance correlation coefficient; equations at the bottom left refer to least-squares simple linear regression. Red line, least-squares simple linear regression line denoted by equation at the bottom of the graph; Blue line, 'y = x'.

absolute mean difference between estimated and measured GFR (Supplementary Figure S6, available at https://doi.org/10.1016/j.esmoop.2022.100401) with smaller limits of agreement for CamGFR v2.

Accuracy, bias and precision

Accuracy (P_{30}), bias MPE and precision MAPE, as defined in the Methods section, were calculated for all patients in both cohorts (Table 3) and for patients included in the sensitivity analysis (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100401).

CamGFR v2 was the most accurate equation with 86.1% and 95.3% of eGFR within 30% of nmGFR. CG-AdBW was the next most accurate of all formulae tested (83.9% and 84.4% of eGFR within 30% of nmGFR at Imperial and Guy's, respectively). After the Wright formula, the unmodified CG estimator was the least accurate of all 10 tested.

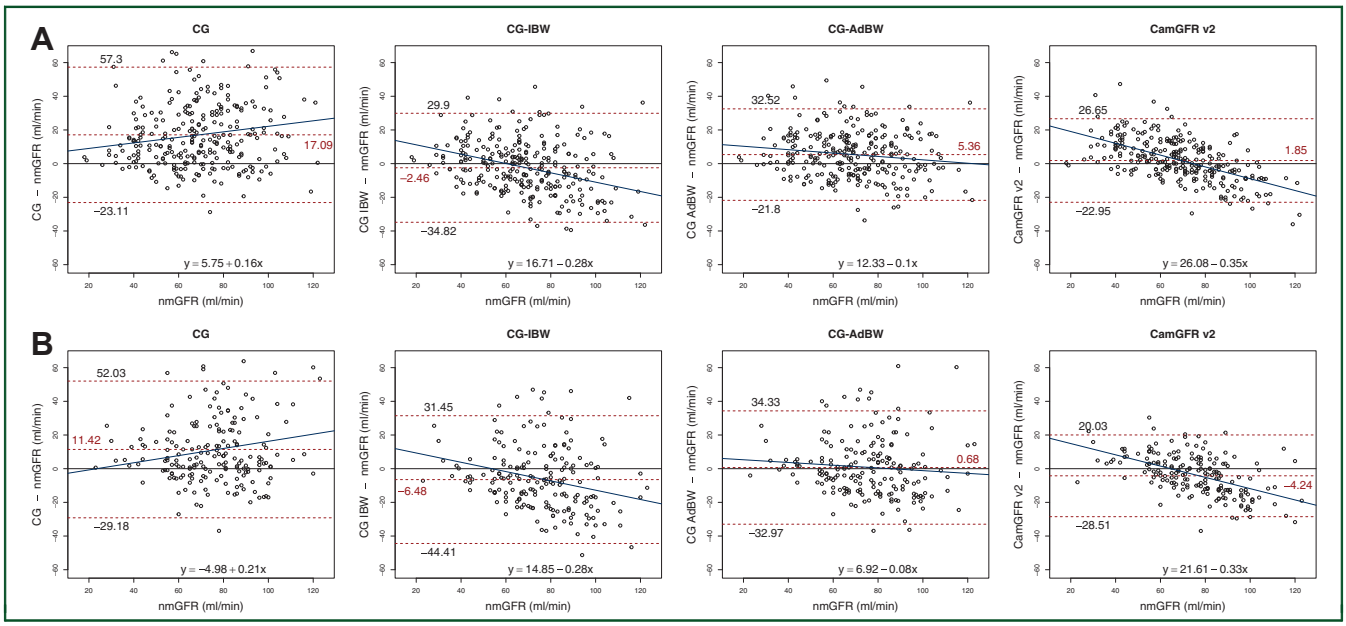

Figure 2. Bland—Altman Plots for agreement between measured and calculated glomerular filtration rate (GFR).
Bland—Altman plots for (A) Imperial cohort, (B) Guy's cohort. Plots show the mean difference, and limits of agreement, between measured GFR (nmGFR) and various Cockcroft—Gault (CG) estimates corrected for ideal body weight (IBW) and adjusted body weight (AdBW) as indicated. Solid black lines represent y = 0. Dashed red lines indicate means and limits of agreement, with red and black text indicating the value of the mean difference and limits of agreement, respectively. Blue lines and black equations represent regression lines and equations, respectively.

Table 3. Accuracy precision and bias for all patients for Imperial (n = 274) and Guy's (n = 192) patients

	CG	CG-IBW	CG-AdBW	CamGFR v2	MDRD (IDMS)	MDRD (IDMS and BSA)	Wright	Jelliffe	Jelliffe (BSA)
P_{30}									
Imperial	61.3	80.6	83.9	86.1	62.4	75.2	46.0	69.7	77.7
Guy's	71.3	72.4	84.4	95.3	71.4	84.9	62.5	78.7	84.4
MPE									
Imperial	19.9	−4.2	7.5	2.2	25.5	15.9	32.8	15.7	12.7
Guy's	8.8	−10.7	−1.6	−4.7	15.7	6.7	21.8	3.4	2.1
MAPE									
Imperial	21.6	16.3	14.7	10.9	26.7	17.1	32.8	19.3	15.3
Guy's	16.3	18.8	13.6	13.2	22.5	15.4	22.3	15.5	12.6

Accuracy, bias and precision represented as p30 (% of eGFR within 30% of nuclear medicine GFR (nmGFR)), median percentage error (MPE) and median absolute percentage error (MAPE), respectively.

BSA, equation modified for body surface area; CG, Cockcroft—Gault corrected for ideal body weight (IBW) or adjusted body weight (AdBW) as indicated; eGFR, estimated glomerular filtration rate; IDMS, isotope dilution mass spectroscopy; MDRD, Modification of Diet in Renal Disease, IDMS version.

CG-IBW, CG-AdBW and CamGFR v2 were the least biased formulae (mean of the absolute MPE across the two cohorts was 7.5%, 4.6% and 3.5%, respectively). Although it performed well in terms of bias, CG-IBW was less precise than CamGFR v2, CG-AdBW and the BSA-adjusted Jelliffe formula. In this regard, CamGFR v2 was the most precise formula with a MAPE of just 10.9% and 13.2% in the Imperial and Guy's cohorts, respectively, with CG-AdBW once again finishing second among all formulae examined.

Accuracy was improved across all formulae in the sensitivity analysis (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100401) but the general pattern across formulae was maintained and, when averaged across the two cohorts, CamGFR v2 and CG-AdBW again showed the highest accuracy and most precision of all the formulae.

Effect on carboplatin dosing

As an exploratory analysis, we examined the effects of this bias and imprecision on the hypothetical dose adjustment following conversion from eGFR to nmGFR-based carboplatin dosing. We initially assumed AUC5 for both estimated and measured values (Table 4, Supplementary Tables S4 and S5, available at https://doi.org/10.1016/j.esmoop.2022.100401).

In a pattern similar to the one used previously, from our primary formulae (unadjusted CG, CG-IBW, CG-AdBW and CamGFR v2), CamGFR v2 was the most accurate for hypothetical carboplatin dosing while CG-AdBW was second. For CamGFR v2, 57.7% and 51.0% of hypothetical nmGFR doses were within 10% of the eGFR dose (rising to 61.3% and 53.8%, respectively, in the sensitivity analysis), while the equivalent figures for CG-AdBW were 48.9% and 49.5% (rising to 52.3% and 52.6%, respectively, in the sensitivity cohort). The least accurate for hypothetical dosing was the Wright formula, with only 21.8% and 38.0% of nmGFR doses falling within 10% of eGFR-calculated dose.

We next looked at the accuracy of formulae when used with AUC6 dosing (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2022.100401) with nmGFR remaining at AUC5. In all formulae, the majority of patients were theoretically overdosed by at least 10% using AUC6-based eGFR dosing. The formula with the lowest propensity for overestimation was CG-IBW.

Standard practice in the UK involves using 'dose banding', where doses are rounded up or down to set values. The National Health Service England (NHS England) provides recommended bands for carboplatin dosing (Supplementary Appendix 3, available at https://doi.org/10.1016/j.esmoop.2022.100401). Thus, we examined the accuracy of hypothetical banded doses, using NHS England recommendations with our primary formulae for GFR estimation (Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2022.100401).

As before, we calculated the percentage of patients whose nmGFR-based dose fell within 10% of their eGFR-based dose. We also calculated the percentage of patients whose nmGFR-based dose exceeded the eGFR-based dose by a given amount (e.g. $>$10%, $>$20%, etc.). However, as an additional metric (given the use of hypothetical banded dosing), we were now able to calculate the percentage of patients whose hypothetical dose was completely unchanged following the switch from nmGFR to eGFR-based dosing.

In both cohorts, the CamGFR v2 formula resulted in the highest percentage of unchanged doses; 32.5% in Imperial cohort and 30.2% in the Guy's cohort. The next most accurate was CG-AdBW (26.3% and 28.6%, respectively). Of note, the unadjusted CG formula produced the same percentage of unchanged doses as CG-AdBW in the Guy's cohort (28.6%); however, CG-AdBW resulted in more nmGFR doses being within 10% of eGFR doses (30.2% compared with 29.7% for unadjusted CG). In the Guy's cohort, CG-AdBW was also less likely to result in overdose by $\geq$30% (2.6% versus 6.3% for unadjusted CG).

As a final observation, we noted that when using dose banding, for any given equation, fewer nmGFR doses fell within 10% of eGFR doses. For example, for CG-AdBW at Imperial and Guy's, 29.9% and 30.2%, respectively, of nmGFR doses fell within 10% of eGFR dose when using dose banding compared with 48.9% and 49.5% when using exact dosing. Despite this, the pattern of accuracy remained similar—that is, CamGFR v2 was the most accurate followed by CG-AdBW across both cohorts.

Table 4. Dose discrepancy between estimated and measured GFR for AUC5 carboplatin dosing

Dose discrepancy	Main analysis [n = 274 (Imperial), n = 192 (Guy's)]								Sensitivity analysis [n = 111 (Imperial), n = 93 (Guy's)]							
	CG		CG-IBW		CG-AdBW		CamGFR v2		CG		CG-IBW		CG-AdBW		CamGFR v2	
	Imperial (%)	Guy's (%)	Imperial (%)	Guy's (%)	Imperial (%)	Guy's (%)	Imperial (%)	Guy's (%)	Imperial (%)	Guy's (%)	Imperial (%)	Guy's (%)	Imperial (%)	Guy's (%)	Imperial (%)	Guy's (%)
< −50%	0.0	0.5	2.2	1.6	0.4	0.5	0	0.5	0	0	2.7	1.1	0.9	0	0	0
< −40%	0.4	1.0	2.2	5.2	0.7	1.6	0.4	0.5	0.9	0	2.7	2.2	0.9	0	0.9	0
< −30%	0.4	1.6	8.0	17.2	1.1	3.1	0.7	2.1	0.9	1.1	9.9	14.0	0.9	1.1	1.8	0
< −20%	1.5	3.1	20.1	30.2	3.6	9.4	4.7	10.9	1.8	1.1	23.4	29.0	4.5	6.5	9.0	7.5
< −10%	4.7	11.5	36.5	45.8	15.7	29.7	15.7	37.0	6.3	10.8	42.3	47.3	19.8	25.8	18.9	35.5
− 10% < dose < 10%	**36.9**	**46.9**	**42.0**	**37.0**	**48.9**	**49.5**	**57.7**	**51.0**	**39.6**	**46.2**	**42.3**	**35.5**	**52.3**	**52.6**	**61.3**	**53.8**
>10%	58.4	41.7	21.5	17.2	35.4	20.8	26.6	12.0	54.1	43.0	15.3	17.2	27.9	21.5	19.8	10.8
>20%	32.1	24.0	7.3	9.9	11.3	11.5	8.8	2.1	23.4	22.6	2.7	10.8	5.4	10.8	4.5	2.2
>30%	11.7	7.8	1.5	2.6	1.8	4.2	1.5	0	7.2	5.4	0.9	1.1	0.9	3.2	0	0
>40%	2.9	1.0	0.0	0	0.7	0	0.7	0	1.8	1.1	0	0	0	0	0	0
>50%	0.7	0	0.0	0	0	0	0	0	0	0	0	0	0	0	0	0

Dose discrepancy between carboplatin doses derived from estimated versus measured GFR (nmGFR). Figures indicate the percentage of patients whose estimated doses exceeded nmGFR doses by the indicated percentage discrepancy.
Percentage of eGFR doses within 10% of nmGFR are highlighted bold for ease of reference.
AUC, area under the curve; CG, Cockcroft–Gault corrected for ideal body weight (IBW) or adjusted body weight (AdBW) as indicated; eGFR, estimated glomerular filtration rate.

Effects of BMI on estimation

As an additional exploratory analysis, we looked at the effect of BMI on bias. We split the data into quartiles of BMI and looked at the trend in percentage error across quartiles (Supplementary Figure S7, available at https://doi.org/10.1016/j.esmoop.2022.100401). For CG formulae we exclusively used unadjusted CG, CG-AdBW or CG-IBW for all patients in that quartile. This differs from the preceding analysis where CG-IBW or CG-AdBW referred to bodyweight adjustment only in those with BMI $\geq$25 kg/m^2. For the Imperial cohort, the 25th percentile was marked by a BMI of 22.9 kg/m^2 and the 75th percentile by a BMI of 29.9 kg/m^2. For Guy's the values were 22.1 and 29.2, respectively.

There was a clear trend where increasing BMI associated with increased positive bias using unadjusted CG (meaning CG tended to overestimate GFR with increasing BMI) and increased negative bias using CG-IBW (GFR progressively underestimated with increasing BMI). This was robust across both cohorts. Conversely, there was no obvious trend when using CG-AdBW or CamGFR to estimate GFR across BMI quartiles.

Finally, we briefly examined the effect of varying BMI threshold on CG-AdBW and CG-IBW. Our previous analyses used a BMI threshold of 25 to partition patients into actual and ideal/AdBW (modified body weight) for CG. Here, we plotted the trend in MPE and MAPE while varying thresholds for BMI cut-off (Supplementary Figure S8, available at https://doi.org/10.1016/j.esmoop.2022.100401). Although the actual values varied across cohorts, the trend was very similar. In both cohorts the least bias occurred when using a BMI cut-off of 21 (7.33% and 0.02% for Imperial and Guy's, respectively) with a monotonic increase in bias after this. For precision (MAPE) using a BMI cut-off of 21 was also the optimum in both cohorts, although the difference in precision between this cut-off and the use of BMI = 25 kg/m^2 was small.

DISCUSSION

We conducted a dual-centre study to investigate the utility of formulae for GFR estimation to guide carboplatin dosing in patients with gynaecological cancers. This is an area marred by uncertainty regarding optimal practice, as evidenced by our small survey, which showed substantial heterogeneity in both the equation used for estimation and whether weight/BSA adjustment was applied. The implications of inaccurate dosing are relevant for both toxicity and efficacy. For this reason, we sought to validate the method used in our centre (CG-AdBW). In addition, we sought to test a novel equation (CamGFR v2) that was developed and validated recently on a large cohort of patients with cancer.[9] To our knowledge, this equation has not been previously tested in a cohort consisting of only patients with gynaecological malignancies.

Using Lin's CCC, we found that among all equations evaluated, the CamGFR v2 and CG-AdBW provided the best agreement with nmGFR. Furthermore, using simple linear

regression, we observed that most equations tended towards underestimation of GFR with each additional unit of nmGFR (i.e. regression slope <1). The only exception was the unadjusted CG equation, which tended to overestimate GFR at all levels of nmGFR, an effect which became worse with increasing nmGFR. This suggests a worrying potential for substantial toxicity using this formula in our centres, especially for those with relatively high nmGFR values.

Similar conclusions were reached when using Bland–Altman plots to interrogate agreement graphically. When averaged across the two cohorts, CG-AdBW and CamGFR v2 produced the lowest mean difference between nmGFR and eGFR. Once again, a negative trend, with increasing propensity to underestimate GFR at high nmGFR values, was seen for most equations. This was more pronounced for CamGFR (slope coefficient −0.33) than for CG-AdBW (slope coefficient −0.08). Although this may suggest potential for underdosing at higher nmGFR values, this may be offset by the tighter limits of agreement using CamGFR v2 compared with CG-AdBW and therefore it is unclear whether such a trend is of clinical significance. Visually, there were fewer outliers with the former equation too. A larger sample of patients may allow better understanding of the nature of our observed trend.

When considering accuracy, bias and precision, both CamGFR v2 and CG-AdBW again performed better than other estimators when considering all three metrics across both cohorts. This translated into accuracy of hypothetical carboplatin dosing. This is likely to lead to fewer dose adjustments for patients who switch from carboplatin dose based on estimated GFR to dosing on nmGFR. This has implications for resource allocation, toxicity and safety. Indeed, when we modelled dose banding, and looked at adjustments following switch from an eGFR-based dosing to an nmGFR-based dosing, CamGFR v2 and CG-AdBW had the highest accuracy when averaged across the two cohorts with 31.4% and 27.5% of doses remaining unchanged, respectively. Nonetheless, this means that even with the best performing formulae, the majority of patients require dose adjustment even with banded dosing.

In general, weight- or BSA-adjusted calculations were superior to those that included neither. We also found that the Wright formulae generally performed very poorly in this cohort of patients and finally, that estimation with AUC6 dosing resulted in overdosing by at least 10% in the majority of cases, again representing a risk of toxicity to patients. This is consistent with recent data suggesting that that the switch to IDMS creatinine a few years ago risks overdosing of carboplatin when using AUC6 dosing.[20] Finally, when using CG to estimate GFR, increasing BMI was associated with increasing bias when using actual or ideal body weight but not when using adjusted weight, which appears agnostic to the influence of BMI by quartiles. Consistent with this, our data suggest that using AdBW in CG calculations for more patients (not just those with BMI $\geq$25 kg/m^2) could be beneficial although this would require further work to validate.

Our survey was limited by its restriction to hospitals in the UK only, and may not be reflective of wider practice in Europe or worldwide. Our study is limited by sample size and the number of centres. Furthermore, many patients had only one creatinine reading within 28 days of nmGFR, although this reflects real-world practice. Further validation would include increasing sample size and widening centre participation. In addition, the two centres used different radiotracers. There is evidence that there is a small, but systematic, difference in GFR measurement between ^{51}Cr-EDTA and 99mTc-DTPA[21] and this may account for some of the systematic difference between the centres. Nonetheless, the trend in observation between the cohorts was consistent, enabling robust conclusions to be made. Finally, we note that we are unable to comment on whether our findings may be extrapolated to other tumour types where carboplatin is routinely used, including in germ-cell and lung tumours, although validation of CamGFR v2 included patients from these cohorts.[8]

We conclude that in our centres nmGFR remains the gold standard for carboplatin dosing. In the absence of this, CG-AdBW is a suitable metric for carboplatin dose estimation. It resulted in better agreement with nmGFR, using various metrics, than both unadjusted and IBW-adjusted CG formulae. In addition, hypothetical carboplatin dosing using CG-AdBW was more accurate than dosing using unadjusted or IBW-adjusted CG. When compared with non-CG formulae, CG-AdBW also tended to produce better agreement with nmGFR, although the CamGFR v2 equation was the one estimator that tended to outperform CG-AdBW.[9] This formula includes a cubic creatinine term and as such is more complex than many of the linear formulae developed on noncancer cohorts. It has been shown (in the original development and validation cohorts) to be more accurate than many formulae including MDRD and CKD-EPI, although was not formally tested against CG-AdBW, the estimator formally recommended by the GOG.[9,10]

Conclusions

In conclusion, individual centres should validate their own methods for GFR estimation but in the absence of empirical evidence, centres should avoid any non-weight-/BSA-adjusted formula, avoid use of the unadjusted CG or Wright formula and avoid dosing on AUC6—all of which have propensity to overestimate GFR and thus potentially cause toxicity. To this end, CG-AdBW is likely to provide high accuracy and precision with low bias, potentially resulting in safer and more efficacious dosing for patients. Finally, CamGFR v2 provides an intriguing new possibility for more accurate GFR estimation, again with the potential to reduce toxicity and/or improve efficacy. It should continue to be investigated further in this cohort of patients.

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ETHICS APPROVAL

Local audit approval for collection of data was obtained. Individual consent to participate was not required.

DATA SHARING

The data underlying this article will be shared on reasonable request to the corresponding author.

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