Received: 20 April 2021 | Revised: 19 August 2021 | Accepted: 3 October 2021

DOI: 10.1111/bcp.15115

SHORT COMMUNICATION

Evaluating prediction methods for glomerular filtration to optimise drug doses in obese and nonobese patients

David Busse[1,2] | Jens Markus Borghardt[3] | David Petroff[4,5] | Alice Pevzner[1] | Christoph Dorn[6] | Nahed El-Najjar[7] | Wilhelm Huisinga[8] | Hermann Wrigge[5,9] | Philipp Simon[4,10] | Charlotte Kloft[1]

[1]Institute of Pharmacy, Department of Clinical Pharmacy and Biochemistry, Freie Universitaet Berlin, Berlin, Germany

[2]Graduate Research Training program PharMetrX, Berlin/Potsdam, Germany

[3]Drug Discovery Sciences, Research DMPK, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany

[4]Integrated Research and Treatment Center (IFB) Adiposity Diseases, University of Leipzig, Leipzig, Germany

[5]Clinical Trial Centre Leipzig, University of Leipzig, Leipzig, Germany

[6]University of Regensburg, Institute of Pharmacy, Regensburg, Germany

[7]Institute of Clinical Microbiology and Hygiene, Faculty of Medicine, University Hospital Regensburg, Regensburg, Germany

[8]University of Potsdam, Institute of Mathematics, Potsdam, Germany

[9]Department of Anesthesiology, Intensive Care and Emergency Medicine, Pain Therapy, Bergmannstrost Hospital Halle, Halle, Germany

[10]Department of Anaesthesiology and Intensive Care Medicine, University of Leipzig, Leipzig, Germany

Correspondence
Charlotte Kloft, Department of Pharmacy, Freie Universitaet Berlin, Kelchstr. 31, 12169, Berlin, Germany.
Email: charlotte.kloft@fu-berlin.de

Funding information
Clinical Trial Centre of the University

Aims: The most suitable method for predicting the glomerular filtration rate (GFR) in obesity is currently debated. Therefore, multiple GFR/creatinine clearance prediction methods were applied to (morbidly) obese and nonobese patients ranging from moderate renal impairment to glomerular hyperfiltration and their predictions were rated based on observed fosfomycin pharmacokinetics, as this model drug is exclusively eliminated via glomerular filtration.

Methods: The GFR/creatinine clearance predictions via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Modification of Diet in Renal Disease (MDRD; indexed and de-indexed by body surface area) and creatinine clearance via the Cockcroft–Gault formula ($CLCR_{CG}$) using different body size descriptors were compared to the fosfomycin clearance (CL_{FOF}) from 30 surgical patients (body mass index = 20.1–52.0 kg m^{-2}), receiving 8000 mg as intravenous infusion.

Results: The concordance between CL_{FOF} and creatinine clearance predictions was highest for $CLCR_{CG}$ employing either ideal body weight or adjusted body weight (if body mass >1.3 ideal body weight; $CLCR_{CG\_ABW\text{-}Schwartz}$, concordance-correlation coefficient [95% confidence interval] = 0.474 [0.156; 0.703], CCC) and GFR predictions via the de-indexed MDRD equation (concordance-correlation coefficient = 0.452 [0.137; 0.685]). The proportion of predicted GFR values within ±30% of the

observed CL_{FOF} (P_{30} = 72.3–76.7%) was only marginally lower than the reported P_{30} in the original CKD-EPI and MDRD publications (P_{30} = 84.1–90.0%).

Conclusion: This analysis represents a successful proof-of-concept for evaluating GFR/creatinine clearance prediction methods: Across all body mass index classes $CLCR_{CG\_ABW\text{-}Schwartz}$ or the de-indexed MDRD were most suitable for predicting creatinine clearance/GFR also in (morbidly) obese, CKD stage <3B individuals in therapeutic use. Their application is proposed in optimising doses for vital therapies in obese patients requiring monitoring of renal function (e.g. methotrexate dosing).

KEYWORDS

creatinine-based equations, drug dosage, fosfomycin, glomerular filtration rate, noncompartmental analysis, obesity prediction of renal function

1 | INTRODUCTION

About 2/3 of all marketed drugs are partly and 1/3 predominantly eliminated by the kidneys.[1,2] Therefore, understanding renal function plays a decisive role in therapy individualisation and therapeutic drug monitoring.[3] Especially for drugs with narrow therapeutic ranges owing to toxicity, e.g. methotrexate, it is essential to assess individual renal clearance for selecting adequate drug dosages to avoid adverse drug reactions or loss of efficacy.[4–6]

The rapidly growing obese population[7] is at particular risk for under- or overdosing of renally eliminated drugs: While obesity can be associated with hyperfiltration, typical comorbidities include chronic kidney disease.[8,9] Thus, accurate determination of renal function in obese individuals is paramount to: (i) prevent erroneous dose adjustment for drugs such as methotrexate requiring lower doses in patients with low renal function[10]; and (ii) to identify patients with hyperfiltration,[11] linked to higher risk of cardiovascular disease and all-cause mortality.[12]

Different options for determining the glomerular filtration rate (GFR) exist, the primary parameter of dominating elimination pathways of renal function,[13] all requiring freely (i.e. unhindered) filtered molecules, which are neither metabolised nor (actively) secreted/reabsorbed in the renal tubuli. For time and cost constraints, creatinine clearance is not routinely measured (e.g. via 24-h urine collection method) but predicted, usually applying the Cockcroft–Gault formula[13] ($CLCR_{CG}$), which is based on measured serum creatinine concentrations. This formula relies on the predictor total body weight (TBW) and was originally determined using data from 236 patients (TBW_{mean} = 72 kg). Due to the often considerably higher TBW of obese patients, it is still debated whether the predictor TBW and therefore the standard Cockcroft–Gault formula represents a meaningful prediction method for obese patients.[14]

Alternative body size-based predictors such as lean (LBW) or adjusted body weight (ABW) have been suggested.[15] Other formulas, e.g. the MDRD (Modification of Diet in Renal Disease) or CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula were designed to predict GFR in patients with chronic kidney disease and are indexed to the standard body surface area (BSA)[9,16] of 1.73 m^2.

What is already known about this subject

- In (morbidly) obese individuals, predictions of the glomerular filtration rate are biased when calculated via the Cockcroft–Gault formula based on total body weight or via the MDRD or CKD-EPI equations.
- Alternative body size descriptors in the Cockcroft–Gault formula and *de-indexation* of glomerular filtration rate calculated via the MDRD and CKD-EPI formulae to individual body surface areas have been suggested as alternative prediction methods, yet no consensus exists in the literature.
- To guide dosing adaptations or to identify patients with hyperfiltration, a single formula is required for simple prediction of renal function in therapeutic use.

What this study adds

- As a model drug to identify the most adequate prediction method of glomerular filtration/creatinine clearance in nonobese and obese individuals, clearance (derived from dense plasma sampling) of fosfomycin, a drug exclusively eliminated through glomerular filtration, without any relevant re-absorption, was exploited.
- Adjusted body weight in the Cockcroft–Gault equation as well as the de-indexed MDRD equation demonstrated highest accuracy and precision among all tested prediction methods and are proposed for therapeutic use to optimise doses in obese patients with drugs that are primarily eliminated via glomerular filtration (e.g. methotrexate dosing).

However, in obese populations, mean BSA deviates substantially from the standard BSA (BSA_{obese} = 2.21 ± 0.22 m^2)[17] and hence *de-indexation* (multiplication of predicted GFR [eGFR] by individual BSA/standard

BSA) has been recommended by the US Food and Drug Administration, the European Medicines Agency and Kidney Disease Improving Global Outcomes organisation for prediction of GFR in obese patients.[8,9]

To identify accurate predictors of GFR/creatinine clearance in obese individuals, previous studies aimed at comparing the agreement between different formulas to calculate creatinine clearance with measured GFR/creatinine clearance. These GFR/creatinine clearance references were either based on creatinine concentrations in serum and cumulative excreted amounts in 24-hour urine collections or accepted GFR references such as tracers measured in plasma, e.g. ^{51}Cr-EDTA.[18–20] However, high imprecision owing to practical difficulties with 24-hour urine collection[13,21] probably compromised the reliability of urine creatinine based reference values.[9] A single study provided ^{51}Cr-EDTA-based clearance values, but only 2 ^{51}Cr-EDTA plasma samples were taken,[9] which required a log-linear regression based on 2 data points per patient and application of empirical correction factors to account for the so-called distribution phase.[22] In the present study, the individual GFR was determined based on dense plasma sampling of the exogenously administered compound **fosfomycin** (no requirement for radioactive labelling and relative ease of application), which is almost exclusively eliminated via glomerular filtration (86.6–94.6% of the dose is recovered unchanged in urine[23–26] and tubular secretion is negligible[27]), much like the gold standards ^{51}Cr-EDTA or iohexol, and has no relevant plasma protein binding.[23] Therefore, the calculated fosfomycin plasma clearance (CL_{FOF}) represents an ideal surrogate of the individual GFR.

This analysis aimed to evaluate the suitability of available prediction methods of GFR/creatinine clearance over a broad body mass index (BMI) range. Various predicted GFR/creatinine clearance values using creatinine-based methods were compared to the individual CL_{FOF}, which served as surrogate reference for the individual glomerular filtration.

2 | METHODS

2.1 | Calculation of the individual reference GFR

This study is an exploratory *posthoc* analysis using data from a clinical study (see Supplementary) investigating the effects of obesity on pharmacokinetics of various antibiotics and analgesics.[28]

Reference renal function was defined as CL_{FOF} estimated via noncompartmental analysis (NCA) using the package PKNCA (Version 0.9.4) in the software R (Version 3.6.0, Vienna/Austria: R Foundation for Statistical Computing). The linear-up log-down approach was selected for calculating the area under the fosfomycin concentration–time curve from time point 0 (start of fosfomycin infusion) to the last sampling time point ($AUC_{0\text{-last}}$). The elimination rate constant (λz) was determined by log-linear regression in the terminal phase, requiring at least 3 data points per patient. Extrapolation of $AUC_{0\text{-last}}$ until infinity ($AUC_{0\text{-}\infty}$) was performed as follows

$$AUC_{0-\infty} = AUC_{0-last} + \frac{C_{last,pred}}{\lambda_z} \quad (1)$$

with $C_{last,pred}$ being the last predicted fosfomycin concentration (based on a log-linear regression). Finally, CL_{FOF} was calculated:

$$CL_{FOF} = \frac{\text{Fosfomycin Dose}}{AUC_{0-\infty}} \quad (2)$$

2.2 | Principal investigator statement

The authors confirm that this is an in silico analysis of data from a clinical trial for which P.S. was the Principal Investigator and that he had direct clinical responsibility for patients.

2.3 | Identification of suitable predictors and prediction methods for GFR

Based on serum creatinine concentrations measured by the IDMS-traceable enzymatic CREP2 assay (Roche Diagnostics, Basel, Switzerland) the predicted GFR/creatinine clearance was calculated: $CLCR_{CG}$ based on the standard predictor TBW[14] and eGFR via the CKD-EPI[29] and MDRD[30] equations (Equation S1-S5).

As alternative predictors of renal function, ideal body weight (IBW),[31] ABW,[32] ABW based on a criterion defined by Schwartz ($ABW_{Schwartz}$)[32–34] and LBW[35] (Equation S6-S9) were used in the Cockcroft–Gault formula to calculate $CLCR_{CG}$. Additionally, the use of body size-based predictors in the Cockcroft–Gault formula was stratified by the World Health Organization-defined BMI categories.[15,36]

De-indexation of GFR via CKD-EPI and MDRD was based on the equation developed by Mosteller due to its wide application[17,37] (Equation S4–5 and S10).

Statistical analyses were performed in R: Concordance between CL_{FOF} *vs.* $CLCR_{CG}$ and eGFR was evaluated by calculating the concordance-correlation coefficient (CCC).[38] Bias and limits of agreement between CL_{FOF} *vs.* $CLCR_{CG}$ and eGFR were determined via Bland–Altman analyses.[39] Magnitude of deviation from the reference (CL_{FOF}) was evaluated by root-mean-square error (RMSE, Equation 1), average-fold-error (AFE, Equation 2) and by the commonly used[9,15,30,40] percentage of $CLCR_{CG}$ and eGFR within ±30% of CL_{FOF} (P_{30}) for all patients. Differences in P_{30} between the prediction methods were evaluated by an exact version of McNemar's test. To evaluate if the deviation from CL_{FOF} might depend on obesity, P_{30} was additionally stratified by obesity status.

$$RMSE = \sqrt{\frac{1}{n}\sum \log\left(\frac{CL_{FOF}}{eGFR\ or\ CLCR_{CG}}\right)^2} \quad (1)$$

$$AFE = 10^{RMSE} \quad (2)$$

2.4 | Identification of glomerular filtration categories

The adequacy of predictors of renal function for dosing adjustments was evaluated using the example for dose adaptations based on the relatively high GFR threshold, associated with methotrexate dose adjustment: Proportions of patients of the patient collective who would require methotrexate dose reductions ($CLCR_{CG}$ ≤ 80 mL/min)[10] were compared between CL_{FOF} and standard predictors as well as alternative predictors of GFR/creatinine clearance. To evaluate which equation performed best to identify patients with hyperfiltration the proportion of patients with eGFR > 130 mL/min[11] was calculated. Finally, it was checked how many of the patients would have been correctly categorised based on the different prediction methods.

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[41]

3 | RESULTS

3.1 | Study population and calculation of reference renal function

The study comprised 30 patients (18 female) with a median (range) age of 51 (26–68) years, serum creatinine concentration of 0.798 (0.588–1.49) mg/dl, BMI of 33.4 (20.1–52.0) kg/m^2, and TBW of 96.0 (61.0–177) kg. 15 patients were obese (BMI ≥ 30 kg/m^2) and 15 non-obese (BMI < 30 kg/m^2).[36] The calculated BSA was 2.18 (1.70–3.10) m^2. In total, 240 (8 per patient) fosfomycin plasma concentrations were available for calculating CL_{FOF} and 3–7 fosfomycin plasma concentrations per patient were used for calculating λz via log-linear regression (R^2 = .738–.999). NCA results were deemed reliable (see Supplementary).

3.2 | Identification of suitable predictors of renal function

Calculated $CL_{FOF,median}$ (range) was 94.0 (32.1–179) mL/min and predicted values according to prediction methods of GFR/creatinine clearance were 127 (66.3–265) mL/min for TBW-based $CLCR_{CG}$, 95.7 (49.9–120) mL/min/1.73 m^2 for eGFR via CKD-EPI and 84.5 (47.0–131) mL/min/1.73 m^2 for eGFR via MDRD (both indexed to BSA = 1.73 m^2). Concordance between CL_{FOF} and these predictors was low (CCC ≤ 0.326, Figure 1A,G,H). For TBW-based $CLCR_{CG}$ prediction bias [95% confidence interval, CI] was higher (−44.6 [−61.9; −27.2] mL/min, Figure 2A) compared to eGFR via CKD-EPI (−8.00 [−3.06; 19.1] mL/min, Figure 1G) and MDRD (+13.9 [2.69; 25.1] mL/min, Figure 1H). The precision of predictions for TBW-based $CLCR_{CG}$ was lower (AFE = 1.71, Table 1) compared to eGFR via CKD-EPI (AFE = 1.41) and MDRD (AFE = 1.44).

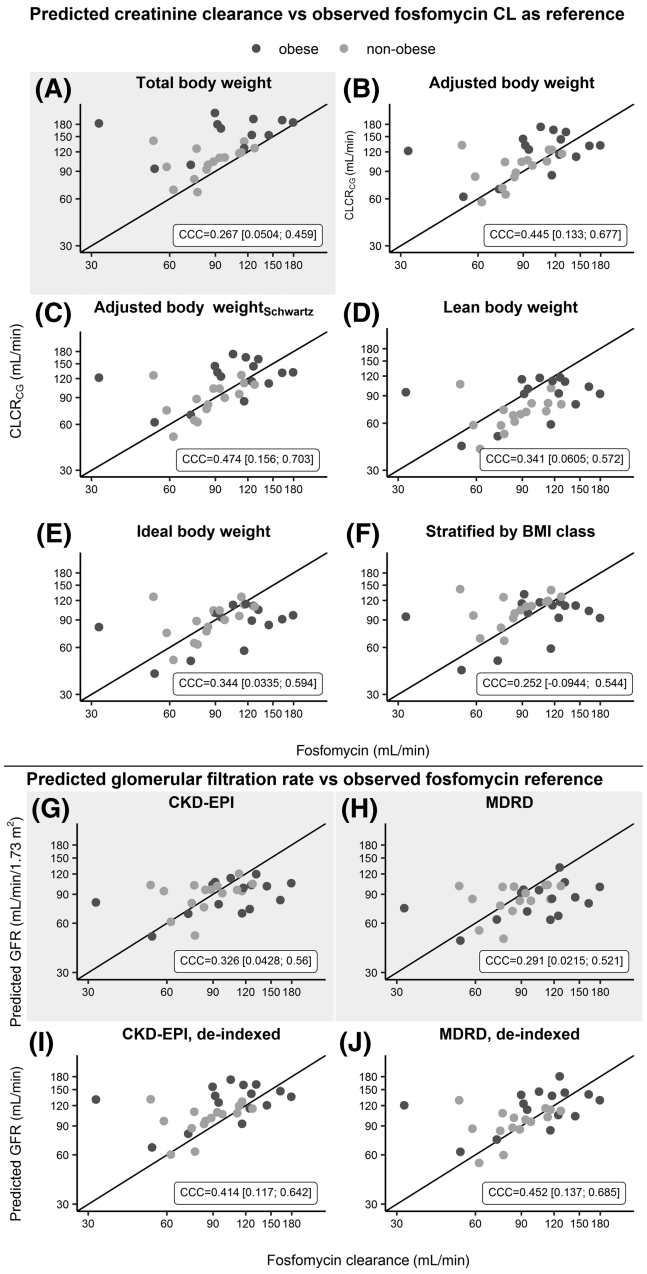

FIGURE 1 Comparison between fosfomycin plasma clearance as reference and creatinine clearance predicted via: (i) the Cockcroft–Gault formula ($CLCR_{CG}$) using different body size-based predictors (A–E, B: ideal body weight or adjusted body weight if body mass >1.3 ideal body weight) or stratification of body size-based predictors by body mass index (BMI) class[15] (F); and (ii) glomerular filtration rate (GFR) predicted via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or Modification of Diet in Renal Disease (MDRD) equation indexed to 1.73 m^2 body surface area (G, H) and de-indexed by individual calculated body surface area[37] (I, J). CCC, Lin's concordance correlation coefficient with 95% confidence interval; CL, clearance

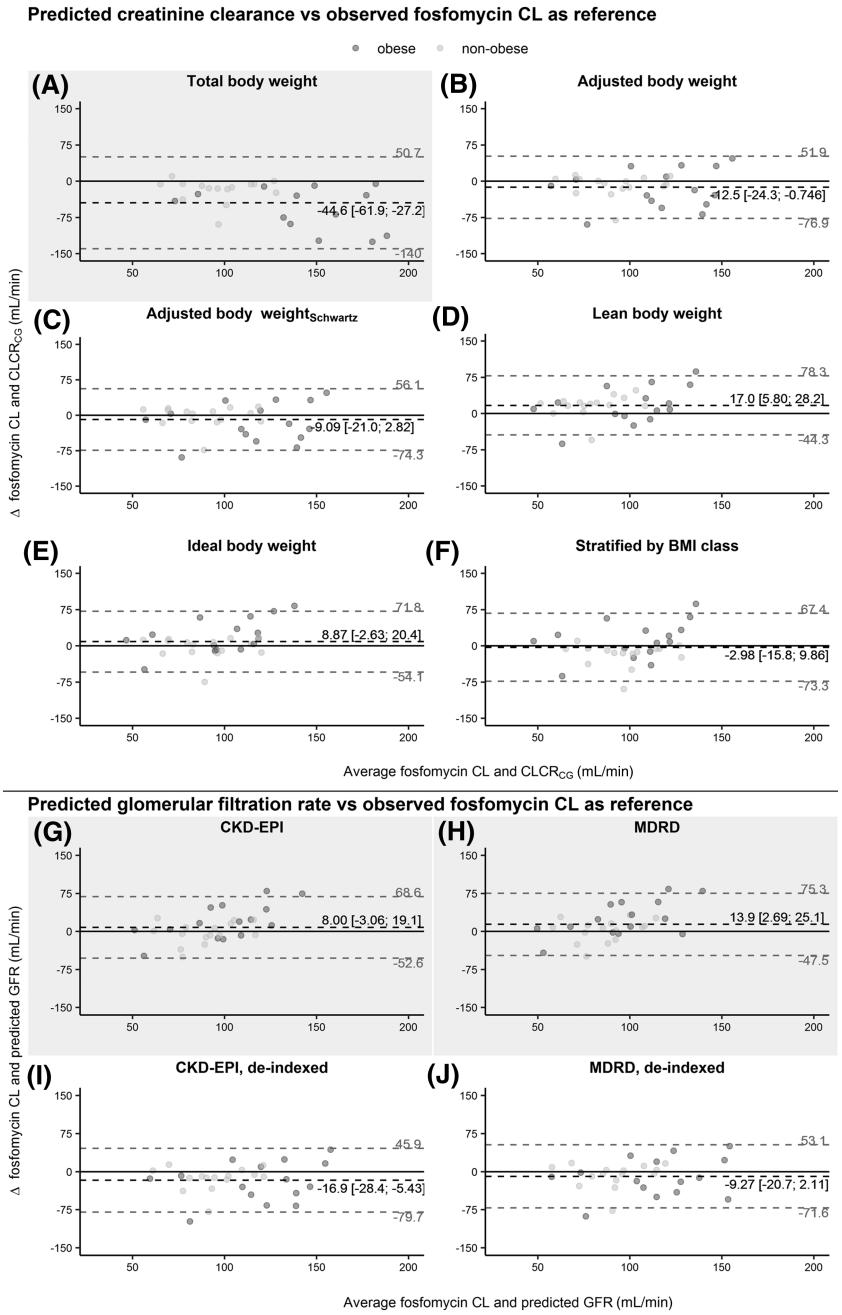

FIGURE 2 Bland–Altman analysis of creatinine clearance predicted via: (i) the Cockcroft–Gault formula ($CLCR_{CG}$) using different body size-based predictors (A–E, B: ideal body weight or adjusted body weight if body mass >1.3 ideal body weight) or stratification of body size–based predictors by body mass index (BMI) class[15] (F); and (ii) glomerular filtration rate (GFR) predicted via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or Modification of Diet in Renal Disease equation (MDRD) indexed to 1.73 m^2 body surface area (G, H) and de-indexed by individual calculated body surface area[37] (I, J). Black dashed line: bias [95% confidence interval]; grey dashed lines: limits of agreement. CL, clearance

Among the alternative prediction methods for GFR, $ABW_{Schwartz}$-based $CLCR_{CG}$ and de-indexed eGFR via MDRD showed highest concordance with CL_{FOF} (CCC ≥ 0.452, Figure 1C, J) and low prediction bias (≤9.27 mL/min, Figure 2C,J). The CIs of both prediction methods included zero, indicating negligible bias ([−21.0; 2.82 mL/min] and [−20.7; 2.11 mL/min], respectively; Figure 2C,J). Comparably low prediction bias [95% CI] was achieved by IBW-based $CLCR_{CG}$ (+9.27 [−20.7; 2.11] mL/min, Figure 2E) or BMI-stratified $CLCR_{CG}$ (−2.98 [−15.8; 9.86] mL/min, Figure 2F). However, the latter showed comparably poor precision of predictions (AFE = 1.48). LBW-based $CLCR_{CG}$ demonstrated low concordance with CL_{FOF} (CCC = 0.341, Figure 1D), and high AFE (1.49).

The P_{30} for $CLCR_{CG}$ and eGFR using all investigated body size descriptors was in overall agreement with a literature-reported analysis aiming at evaluating prediction methods of GFR over a wide BMI range[42]: After stratification by obesity status, P_{30} for each prediction method was 10.0–58.4% lower in obese *vs.* nonobese patients. TBW-based $CLCR_{CG}$ resulted in the highest discrepancy between obese and nonobese patients (58.4%). The difference in P_{30} between populations was lower for de-indexed eGFR via MDRD (16.6%) compared to $ABW_{Schwartz}$-based $CLCR_{CG}$ (35.7%).

TABLE 1 Summary statistics for the comparison between the reference (fosfomycin plasma clearance) and creatinine clearance predicted via the Cockcroft–Gault formula or predicted glomerular filtration rate including obese and nonobese individuals over a large range of body mass index

Method	RMSE	AFE	P_{30}
$CLCR_{CG}$ based on:			
-Total body weight	0.234	1.71	56.7%
-Adjusted body weight	0.162	1.45	70.0%
-Adjusted body $weight_{Schwartz}$[a]	0.160	1.44	76.7%
-Ideal body weight	0.156	1.43	76.7%
-Lean body weight	0.174	1.49	63.3%
-BMI class stratified	0.168	1.48	70%
eGFR based on:			
-CKD-EPI	0.149	1.41	66.7%
-MDRD	0.159	1.44	66.7%
-CKD-EPI, de-indexed	0.170	1.48	70.0%
-MDRD, de-indexed	0.158	1.44	73.3%

AFE, average fold error; BMI, body mass index, $CLCR_{CG}$, creatinine clearance predicted via the Cockcroft–Gault formula using different body size descriptors or stratification of body size descriptors by BMI class[15]; eGFR, glomerular filtration rate predicted via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or Modification of Diet in Renal Disease equation (MDRD) de-indexed by individual calculated body surface area[37]; P_{30}: proportion of patients within ±30% deviation from reference glomerular filtration rate; RMSE, root mean squared error; SD, standard deviation.

[a]$CLCR_{CG}$ based on ideal body weight (IBW) or adjusted body weight (if body mass >1.3 IBW), see Equation S8.

The odds ratios (OR) of P_{30} for ABW- and IBW-based CLCR were >1 *vs.* all other prediction methods. However, 95% CIs of OR were broad and included 1 for each comparison (except for $ABW_{Schwartz}$- *vs.* TBW-based CLCR; Table S2).

3.3 | Identification of glomerular filtration categories

For the example of methotrexate dose adjustments, 9/30 patients fell into the category creatinine clearance≤80 mL/min (threshold dose reduction) as calculated by CL_{FOF}, but a much lower proportion was identified by TBW-based $CLCR_{CG}$ (2/30; Table S1). Proportions calculated by $ABW_{Schwartz}$-based $CLCR_{CG}$ (7/30, 1 false positive) and eGFR via MDRD (11/30 with 5 false positive; de-indexed: 4/30) were closer to the reference. Similarly, for patients categorised as *hyperfiltrators* (eGFR>130 mL/min) according to the reference proportion of patients (4/30), the agreement was greatest for $ABW_{Schwartz}$-based $CLCR_{CG}$ (8/30 with 5 false positive; Table S1) and eGFR via MDRD (1/30 with 1 false positive; de-indexed: 6/30 with 4 false positive) but was largely overpredicted using TBW-based $CLCR_{CG}$ (14/30).

4 | DISCUSSION

Fosfomycin clearance based on dense plasma sampling was chosen as a reliable reference of renal function to permit identification of good prediction methods and predictors of glomerular filtration/creatinine clearance for nonobese and obese individuals alike. Whereas the commonly employed TBW-based $CLCR_{CG}$ overpredicted renal function, $ABW_{Schwartz}$-based $CLCR_{CG}$ and de-indexed eGFR via MDRD provided a low bias and the highest agreement with the reference renal function.

Fosfomycin clearance calculation was based on dense plasma sampling, which can be expected to provide more reliable and accurate individual reference renal function values than the commonly employed references based on single measurements of serum creatinine concentration and 24-hour urine concentrations.[18,43,44] In the past, identification of an adequate value for GFR in the obese has been based on a small number of measurements of exogenous markers over time (^{51}Cr-EDTA, iohexol). These studies were not based on dense sampling schedules and populations did not include normal-weight individuals and could thus not evaluate if a single formula was adequate over a large range of BMI values including nonobese individuals.[9,45] In contrast, our study represents a proof-of-concept for employing exposure data from an exclusively renally eliminated drug in both obese and nonobese individuals to evaluate predictors and prediction methods of GFR/creatinine clearance. The predictive performance of GFR/creatinine clearance prediction methods has been evaluated before via the elimination of drugs predominantly eliminated via glomerular filtration, such as vancomycin[46,47] (critically ill patients) or gentamicin[48] (geriatric patients). However, accuracy of elimination of vancomycin as GFR/creatinine clearance reference in obese and nonobese patients was compromised by tubular secretion and reabsorption.[49]

We confirmed the overprediction of creatinine clearance by TBW-based $CLCR_{CG}$ reported over a large range of BMI values.[50] Nevertheless, this method is still recommended by the Food and Drug Administration and European Medicines Agency. A reported improvement of bias and precision by using LBW-based $CLCR_{CG}$ in obese individuals[43] or for nonobese and obese individuals by stratification via BMI classes[15] could not be confirmed in our study. However, stratification by BMI[15] might be more accessible to clinicians than e.g. $ABW_{Schwartz}$ given the wide acceptance of BMI for categorisation of obesity classes.[36] Rather, our finding that the non-body size-dependent eGFR via MDRD showed low overall bias and highest precision was in line with previous investigations.[9,51] A previously reported tendency for overpredicting the GFR by MDRD at normal to high reference GFR values could not be confirmed.[52,53]

Notably, accuracy of MDRD derived GFR in individuals with normal kidney function has been demonstrated to be reduced compared to the CKD-EPI formula.[29] Reduced accuracy of predicted renal function via MDRD *vs.* the Cockcroft–Gault formula has been reported in diverse populations, when applying standardised creatinine concentrations.[54]

Among the body size-dependent formulas, $ABW_{Schwartz}$-based $CLCR_{CG}$ was the most adequate method of GFR/creatinine clearance, being in line with published results.[9,18] Accuracy was similar to literature-reported values for $ABW_{Schwartz}$-based $CLCR_{CG}$ (P_{30} = 76.6% *vs.* P_{30} = 69.8[15]) and de-indexed eGFR via MDRD (P_{30} = 73.3% *vs.* 73.7%[15]). Overall, accuracy was close to reported accuracy for the original MDRD (P_{30} = 76.6% *vs.* P_{30} = 90.0%[30]) and CKD-EPI equations (P_{30} = 73.3% *vs.* P_{30} = 84.6%[40]) in nonobese individuals, suggesting adequacy for clinical use. However, in our analysis no patients with a chronic kidney disease stage ≥3B and a relatively low patient number (30 patients) were included, which only allowed identification of trends in P_{30} values. Further studies with more obese and nonobese patients, including patients with severe chronic kidney disease are necessary to evaluate conclusively, which prediction method of renal function is most adequate in obese patients. Inclusion of the gold standard ^{51}Cr-EDTA or iohexol as reference for GFR in such studies will allow confirming the adequacy of exogenously administered compounds, such as fosfomycin, as alternative references of renal function. These could also evaluate if measurement of serum cystatin C in addition to serum creatinine concentrations[55] improves precision and accuracy of GFR/creatinine clearance prediction in obese patients.

Through an example for dose adaptations based on a relatively high GFR threshold, (methotrexate), we could show that the choice of the predictor and method to predict GFR would have a relevant impact on clinical decision making. The high failure rate in our example when dosing methotrexate according to TBW-based $CLCR_{CG}$ (23.3% of patients) was largely reduced by using $ABW_{Schwartz}$-based $CLCR_{CG}$ (13.3% of patients) or eGFR via MDRD (16.7% of patients) instead. For classification of patients as hyperfiltrators, both alternative prediction methods resulted in high false-positive rates ($ABW_{Schwartz}$-based $CLCR_{CG}$: 5/8; eGFR via MDRD 4/6), compromising their use for diagnostic purposes.

In conclusion, based on a reference renal function calculated by rich PK data for fosfomycin, a drug almost exclusively eliminated via glomerular filtration, we showed that the use of $ABW_{Schwartz}$ in the Cockcroft–Gault formula or de-indexed eGFR by MDRD equation led to the lowest bias and highest precision among evaluated predictors and prediction methods of GFR/creatinine clearance over a wide BMI range. Their application is proposed in obese patients for improving drug dosing decision-making, which require accurate GFR monitoring, such as for glucose-lowering (e.g. metformin) anticonvulsant (e.g. gabapentin), anticonvulsant and analgesic (e.g. pregabalin) and anti-Parkinson (e.g. amantadine) treatment.

ACKNOWLEDGEMENTS

We thank the team of the Clinical Trial Centre of the University of Leipzig for generating the data by organisational support, study promotion, and on-site monitoring of the clinical trial, to Christiane Prettin for the excellent study management and to Frank Mehner, Nancy Neumann, Sophie Hochstädt, Melanie Simon, Sven Walther and Jana Heyde for their help in data acquisition. We thank Ferdinand Weinelt, Luis Ilia and Dr Robin Michelet for fruitful discussions.

COMPETING INTERESTS

C.K. and W.H. report grants from an industry consortium (AbbVie Deutschland GmbH & Co. KG, AstraZeneca GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, Grünenthal GmbH, F. Hoffmann-La Roche Ltd, Merck KGaA and SANOFI) for the PharMetrX PhD program. C.K. reports grants for the Innovative Medicines Initiative-Joint Undertaking (DDMoRe), Diurnal Ltd., the Federal Ministry of Education and Research within the Joint Programming Initiative on Antimicrobial Resistance Initiative (JPIAMR) and from the European Commission within in the Horizon 2020 framework programme (FAIR), all outside the submitted work. J.B. is an employee of Boehringer Ingelheim Pharma GmbH & Co. KG and his contribution was based on an industry mentorship for D.B. outside his regular work. H.W. received research funding, lecture fees, and technical support from Dräger Medical, Lübeck, Germany; funding from Pfizer (Investigator Initiated Trial Program), Berlin, Germany; funding and lecture fees from InfectoPharm, Heppenheim, Germany; lecture fees from GE Healthcare, Freiburg, Germany, lecture fees from Maquet, Rastatt, Germany; lecture fees from MSD, Konstanz, Germany, and advisory board honoraria from Liberate Medical, KY, USA. The other authors declare that they have no competing interests.

CONTRIBUTORS

D.B., J.B., D.P. and C.K. designed the data analysis. P.S. and D.P. designed and conducted the clinical study and N.E. and C.D. performed assays. D.B., J.B., D.P. and C.K. performed the data analysis. D.B., J.B., P.S., D.P., C.D., W.H., H.W. and C.K. discussed the results. D.B., J.B., D.P., A.P. and C.K. drafted the manuscript. All authors commented on and approved the manuscript.

DATA AVAILABILITY STATEMENT

The datasets may be provided upon reasonable request.

ORCID

David Busse https://orcid.org/0000-0003-2738-7797
Jens Markus Borghardt https://orcid.org/0000-0001-7000-9308
David Petroff https://orcid.org/0000-0002-6916-1465
Wilhelm Huisinga https://orcid.org/0000-0002-5249-3914
Philipp Simon https://orcid.org/0000-0003-2696-3254

REFERENCES

1. Barreto EF, Rule AD, Murad MH, et al. Prediction of the Renal Elimination of Drugs With Cystatin C vs Creatinine: A Systematic Review. *Mayo Clin Proc*. 2019;94(3):500-514. https://doi.org/10.1016/j.mayocp.2018.08.002
2. Varma MVS, Feng B, Obach RS, et al. Physicochemical Determinants of Human Renal Clearance. *J Med Chem*. 2009;52(15):4844-4852. https://doi.org/10.1021/jm900403j
3. Gross AS. Best practice in therapeutic drug monitoring. *Br J Clin Pharmacol*. 1998;46(2):95-99. https://doi.org/10.1046/j.1365-2125.1998.00770.x
4. Cheymol G. Effects of Obesity on Pharmacokinetics. *Clin Pharmacokinet*. 2000;39(3):215-231. https://doi.org/10.2165/00003088-200039030-00004

5. Ehmann L, Zoller M, Minichmayr IK, et al. Development of a dosing algorithm for meropenem in critically ill patients based on a population pharmacokinetic/pharmacodynamic analysis. *Int J Antimicrob Agents*. 2019;43(3):309-317. https://doi.org/10.1016/j.ijantimicag.2019.06.016
6. Minichmayr IK, Roberts JA, Frey OR, Roehr AC, Kloft C, Brinkmann A. Development of a dosing nomogram for continuous-infusion meropenem in critically ill patients based on a validated population pharmacokinetic model. *J Antimicrob Chemother*. 2018;73(5):1330-1339. https://doi.org/10.1093/jac/dkx526
7. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. *Metabolism*. 2019;92:6-10. https://doi.org/10.1016/j.metabol.2018.09.005
8. Pai MP. Estimating the Glomerular Filtration Rate in Obese Adult Patients for Drug Dosing. *Adv Chronic Kidney Dis*. 2010;17(5):e53-e62. https://doi.org/10.1053/j.ackd.2010.05.010
9. Bouquegneau A, Vidal-Petiot E, Moranne O, et al. Creatinine-based equations for the adjustment of drug dosage in an obese population. *Br J Clin Pharmacol*. 2015;81(2):349-361. https://doi.org/10.1111/bcp.12817
10. Hospira UK Ltd. Summary of Product Characteristics Methotrexate. https://www.medicines.org.uk/emc/product/6789/smpc/print#gref. Published 2019. Accessed August 14, 2021.
11. Cachat F, Combescure C, Cauderay M, Girardin E, Chehade H. A Systematic Review of Glomerular Hyperfiltration Assessment and Definition in the Medical Literature. *Clin J am Soc Nephrol*. 2015;10(3):382 LP-389. https://doi.org/10.2215/CJN.03080314
12. Kanbay M, Ertuglu LA, Afsar B, et al. Renal hyperfiltration defined by high estimated glomerular filtration rate: A risk factor for cardiovascular disease and mortality. *Diabetes Obes Metab*. 2019;21(11):2368-2383. https://doi.org/10.1111/dom.13831
13. Traynor J, Mactier R, Geddes CC, Fox JG. How to measure renal function in clinical practice. *BMJ*. 2006;333(7571):733-737. https://doi.org/10.1136/bmj.38975.390370.7C
14. Cockcroft DW, Gault MH. Prediction of Creatinine Clearance from Serum Creatinine. *Nephron*. 1976;16(1):31-41.
15. Park EJ, Pai MP, Dong T, et al. The influence of body size descriptors on the estimation of kidney function in normal weight, overweight, obese, and morbidly obese adults. *Ann Pharmacother*. 2012;46(3):317-328. https://doi.org/10.1345/aph.1Q374
16. Shemesh O, Golbetz H, Kriss JP, Myers BD. Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int*. 1985;28(5):830-838. https://doi.org/10.1038/ki.1985.205
17. Verbraecken J, Van De Heyning P, De Backer W, Van Gaal L. Body surface area in normal-weight, overweight, and obese adults. A comparison study. *Metabolism*. 2006;55(4):515-524. https://doi.org/10.1016/j.metabol.2005.11.004
18. Winter MA, Guhr KN, Berg GM. Impact of various body weights and serum creatinine concentrations on the bias and accuracy of the Cockcroft-Gault equation. *Pharmacotherapy*. 2012;32(7):604-612. https://doi.org/10.1002/j.1875-9114.2012.01098.x
19. Hahn T, Yao S, Dunford LM, et al. A Comparison of Measured Creatinine Clearance versus Calculated Glomerular Filtration Rate for Assessment of Renal Function before Autologous and Allogeneic BMT. *Biol Blood Marrow Transplant*. 2009;15(5):574-579. https://doi.org/10.1016/j.bbmt.2009.01.015
20. Bouquegneau A, Vidal-Petiot E, Vrtovsnik F, et al. Modification of Diet in Renal Disease versus Chronic Kidney Disease Epidemiology Collaboration equation to estimate glomerular filtration rate in obese patients. *Nephrol Dial Transplant*. 2013;28(suppl_4):iv122-iv130. https://doi.org/10.1093/ndt/gft329
21. Waller DG, Fleming JS, Ramsey B, Gray J. The accuracy of creatinine clearance with and without urine collection as a measure of glomerular filtration rate. *Postgrad Med J*. 1991;67(783):42-46. https://doi.org/10.1136/pgmj.67.783.42
22. Fleming JS, Zivanovic MA, Blake GM, Burniston M, Cosgriff PS. Guidelines for the measurement of glomerular filtration rate using plasma sampling. *Nucl Med Commun*. 2004;25(8):759-769. https://doi.org/10.1097/01.mnm.0000136715.71820.4a
23. Bergan T, Thorsteinsson SB, Albini E. Pharmacokinetic Profile of Fosfomycin Trometamol. *Chemotherapy*. 1993;39(5):297-301. https://doi.org/10.1159/000239140
24. Bergan T. Degree of absorption, pharmacokinetics of fosfomycin trometamol and duration of urinary antibacterial activity. *Infection*. 1990;18(2):S65-S69. https://doi.org/10.1007/BF01643430
25. Goto M, Sugiyama M, Nakajima S, Yamashina H. Fosfomycin kinetics after intravenous and oral administration to human volunteers. *Antimicrob Agents Chemother*. 1981;20(3):393-397. https://doi.org/10.1128/AAC.20.3.393
26. Kwan KC, Wadke DA, Foltz EL. Pharmacokinetics of Phosphonomycin in Man I:Intravenous Administration. *J Pharm Sci*. 1971;60(5):678-685. https://doi.org/10.1002/jps.2600600504
27. Patel SS, Balfour JA, Bryson HM. Fosfomycin Tromethamine. *Drugs*. 1997;53(4):637-656. https://doi.org/10.2165/00003495-199753040-00007
28. Simon P, Petroff D, Dorn C, et al. Measurement of soft tissue drug concentrations in morbidly obese and non-obese patients – A prospective, parallel group, open-labeled, controlled, phase IV, single center clinical trial. *Contemp Clin Trials Commun*. 2019;15:100375. https://doi.org/10.1016/j.conctc.2019.100375
29. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612. https://doi.org/10.7326/0003-4819-150-9-200905050-00006
30. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006;145(4):247-254. https://doi.org/10.7326/0003-4819-145-4-200608150-00004
31. McCarron MM, Devine BJ. Clinical pharmacy: case studies: case number 25 gentamicin therapy. *Drug Intell Clin Pharm*. 1974;8(11):650-655. https://doi.org/10.1177/106002807400801104
32. Schwartz SN, Pazin GJ, Lyon JA, Ho M, Pasculle AW. A controlled investigation of the pharmacokinetics of gentamicin and tobramycin in obese subjects. *J Infect Dis*. 1978;138(4):499-505.
33. Hicks C, Trickett A, Kwan YL, Ramanathan S. The use of adjusted ideal body weight for overweight patients undergoing HPC mobilisation for autologous transplantation. *Ann Hematol*. 2012;91(11):1795-1801. https://doi.org/10.1007/s00277-012-1523-1
34. Krenitsky J. Adjusted Body Weight, Pro: Evidence to Support the Use of Adjusted Body Weight in Calculating Calorie Requirements. *Nutr Clin Pract*. 2005;20(4):468-473. https://doi.org/10.1177/0115426505020004468
35. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. *Clin Pharmacokinet*. 2005;44(10):1051-1065. https://doi.org/10.2165/00003088-200544100-00004
36. World Health Organization. Body mass index - BMI. http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi. Published 2021. Accessed February 10, 2021.
37. Mosteller RD. Simplified Calculation of Body-Surface Area. *N Engl J Med*. 1987;317(17):1098. https://doi.org/10.1056/NEJM198710223171717
38. Lin LI-K. A Concordance Correlation Coefficient to Evaluate Reproducibility. *Biometrics*. 1989;45(1):255-268. https://doi.org/10.2307/2532051
39. Altman DG, Bland JM. Measurement in Medicine: The Analysis of Method Comparison Studies. *J R Stat Soc Ser D (the Stat.)*. 1983;32(3):307-317. https://doi.org/10.2307/2987937
40. Stevens LA, Coresh J, Schmid CH, et al. Estimating GFR Using Serum Cystatin C Alone and in Combination With Serum Creatinine: A

Pooled Analysis of 3,418 Individuals With CKD. *Am J Kidney Dis*. 2008;51(3):395-406. https://doi.org/10.1053/j.ajkd.2007.11.018

41. Alexander SPH, Fabbro D, Kelly E, et al. THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: Enzymes. *Br J Pharmacol*. 2019;176(S1): S297-S396. https://doi.org/10.1111/bph.14752
42. Park EJ, Pai MP, Dong T, et al. The influence of body size descriptors on the estimation of kidney function in normal weight, overweight, obese, and morbidly obese adults. *Ann Pharmacother*. 2012;46: (1542–6270 [Electronic]):317-328. https://doi.org/10.1345/aph.1Q374
43. Demirovic JA, Pai AB, Pai MP. Estimation of creatinine clearance in morbidly obese patients. *Am J Heal Pharm*. 2009;66(7):642-648. https://doi.org/10.2146/ajhp080200
44. Dionne RE, Bauer LA, Gibson GA, Griffen WO, Blouin RA. Estimating creatinine clearance in morbidity obese patients. *Am J Hosp Pharm*. 1981;38(6):841-844.
45. Friedman AN, Strother M, Quinney SK, et al. Measuring the Glomerular Filtration Rate in Obese Individuals without Overt Kidney Disease. *Nephron Clin Pract*. 2010;116(3):c224-c234. https://doi.org/10.1159/000317203
46. Conil JM, Georges B, Breden A, et al. Estimation of Glomerular Filtration Rate to Adjust Vancomycin Dosage in Critically Ill Patients: Superiority of the Chronic Kidney Disease Epidemiology Collaboration Equation? *Anaesth Intensive Care*. 2014;42(2):178-184. https://doi.org/10.1177/0310057X1404200203
47. Abramavicius S, Galaune V, Tunaityte A, et al. The Glomerular Filtration Rate Estimators in the Pharmacokinetic Modelling in Acute Kidney Injury: An Observational Study. *Antibiot (Basel, Switzerland)*. 2021;10(2):158. https://doi.org/10.3390/antibiotics10020158
48. Charhon N, Neely MN, Bourguignon L, Maire P, Jelliffe RW, Goutelle S. Comparison of four renal function estimation equations for pharmacokinetic modeling of gentamicin in geriatric patients. *Antimicrob Agents Chemother*. 2012;56(4):1862-1869. https://doi.org/10.1128/AAC.05634-11
49. Nakamura T, Hashimoto Y, Kokuryo T, Inui K-I. Effects of Fosfomycin and Imipenem/Cilastatin on Nephrotoxicity and Renal Excretion of Vancomycin in Rats. *Pharm Res*. 1998;15(5):734-738. https://doi.org/10.1023/A:1011971019868
50. Wuerzner G, Bochud M, Giusti V, Burnier M. Measurement of glomerular filtration rate in obese patients: Pitfalls and potential consequences on drug therapy. *Obes Facts*. 2011;4(3):238-243. https://doi.org/10.1159/000329547
51. Rigalleau V, Lasseur C, Perlemoine C, et al. Cockcroft-Gault formula is biased by body weight in diabetic patients with renal impairment. *Metabolism*. 2006;55(1):108-112. https://doi.org/10.1016/j.metabol.2005.07.014
52. Hallan S, Åsberg A, Lindberg M, Johnsen H. Validation of the modification of diet in renal disease formula for estimating GFR with special emphasis on calibration of the serum creatinine assay. *Am J Kidney Dis*. 2004;44(1):84-93. https://doi.org/10.1053/j.ajkd.2004.03.027
53. Vervoort G, Willems HL, Wetzels JFM. Assessment of glomerular filtration rate in healthy subjects and normoalbuminuric diabetic patients: validity of a new (MDRD) prediction equation. *Nephrol Dial Transplant*. 2002;17(11):1909-1913. https://doi.org/10.1093/ndt/17.11.1909
54. Stevens LA, Manzi J, Levey AS, et al. Impact of Creatinine Calibration on Performance of GFR Estimating Equations in a Pooled Individual Patient Database. *Am J Kidney Dis*. 2007;50(1):21-35. https://doi.org/10.1053/j.ajkd.2007.04.004
55. Inker LA, Schmid CH, Tighiouart H, et al. Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. *N Engl J Med*. 2012;367(1):20-29. https://doi.org/10.1056/NEJMoa1114248

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Busse D, Borghardt JM, Petroff D, et al. Evaluating prediction methods for glomerular filtration to optimise drug doses in obese and nonobese patients. *Br J Clin Pharmacol*. 2022;88(6):2973-2981. doi:10.1111/bcp.15115