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*Research article*

# A retrospective study comparing creatinine clearance estimation using different equations on a population-based cohort

**Abigail Ferreira[1,2], Rui Lapa[2] and Nuno Vale[1,3,*]**

[1] OncoPharma Research Group, Center for Health Technology and Services Research (CINTESIS), Rua Dr. Plácido da Costa, Porto 4200-450, Portugal
[2] LAQV/REQUIMTE, Laboratory of Applied Chemistry, Department of Chemical Sciences, Faculty of Pharmacy, University of Porto, Rua de Jorge Viterbo Ferreira, 228, Porto 4050-313, Portugal
[3] Department of Community Medicine, Health Information and Decision (MEDCIDS), Faculty of Medicine, University of Porto, Al. Prof. Hernâni Monteiro, Porto 4200-319, Portugal

* **Correspondence:** Email: nunovale@med.up.pt; Tel: +351225513622; Fax: +351225513668.

**Abstract:** Renal elimination is an important part of drugs' excretion. At the same time, renal function can be impaired as a side effect of medication, particularly during prolonged treatments. Thus, the assessment of patients' renal function is of major consequence, especially in cases where the therapeutic regimen is adjusted taking into consideration renal clearance. Serum creatinine concentration is the most common indicator of renal clearance, since the most accurate indicator, glomerular filtration rate (GFR), is not easily measured. Using equations developed over the last decades, creatinine clearance ($CL_{Cr}$) is readily estimated taking into account patients' biological sex, age, body composition, and sometimes race. In this work, differences in estimated $CL_{Cr}$ between different equations were studied and the influence of some patients' characteristics evaluated. Data collected from 82 inpatients receiving antibiotic therapy was analyzed and $CL_{Cr}$ was estimated using a total of 12 equations. Patients were stratified according to their sex, age, and body composition to shed some light on the impact of these parameters in the estimations of renal function. More variability between estimation methods was highlighted (a) in patients between 51 and 60 years old, (b) within the normal body mass index group, and (c) in patients with serum creatinine levels below normal criteria. Furthermore, the Cockcroft-Gault equation considering lean body weight produced lower estimated $CL_{Cr}$ in almost all groups.

**Keywords:** creatinine clearance estimation; renal function; therapeutic drug monitoring (TDM); antibiotics; Cockcroft-Gault formula; Jelliffe formula; Wright formula; Corcoran-Salazar formula

## 1. Introduction

Kidneys play an important role in the elimination of many drugs, including antibiotics. Renal function varies according to age, sex, body size, and race, is influenced by strenuous physical activity, diet, and consumption of red meat, certain herbs, and supplements, and is altered during pregnancy. Most importantly, it can be impaired as a collateral effect of medication, which is particularly significant during prolonged treatments. As such, evaluating patients' renal function is a key component of therapeutic drug monitoring (TDM), along with examining peak and trough plasma levels of the drug. Glomerular filtration rate (GFR) is regarded as a crucial indicator of kidney function. Generally, a GFR above 90 mL/min indicates a normal kidney function [1]. Unfortunately, GFR is not easily determined in a clinical setting; instead, renal function is often estimated from serum creatinine concentration (SCr), using numerous equations developed over the last decades and demographic parameters as sex, body size, age, and race [2,3]. SCr is rapidly determined, and these estimations can be readily calculated. However, these equations were derived from data collected from very diverse study populations, and there is neither a universal nor subpopulation-specific standard equation. As such, clinicians must decide how to calculate this estimation (what equation to use) or most frequently, follow what the institution has established. Since each equation results in dissimilar estimated clearance for the same individual, therapeutic adjustment can be significantly different according to the chosen method.

Antibiotics are one of the most prescribed drugs. Monitoring patients and appropriately adjusting the dose of the antibiotic or the treatment regimen is important to optimize the clinical outcome, reduce the risk of toxic side effects and avoid serious deterioration of renal function associated with increased plasmatic levels and drug accumulation while aiming at improving efficacy, and also due to great inter-individual variability. This can also help limit antibiotic resistance.

**Table 1.** Pharmacokinetic (PK) properties of antibiotics amikacin, gentamicin, tobramycin, and vancomycin [4–10].

| PK | Amikacin | Gentamicin | Tobramycin | Vancomycin |
|---|---|---|---|---|
| Hydrophilicity | Hydrophilic | | | |
| Metabolism | Eliminated unchanged in urine | | | |
| $F_{up}$ | > 90% | > 70% | > 70% | 50–90% |
| $T_{1/2}$ | 2–3 h | 2–3 h | 2–3 h | ~6 h (4–11 h) |
| $V_c$ | ~0.34 L/kg | 0.2–0.3 L/kg | 0.2–0.3 L/kg | 0.4–1 L/kg |
| Clearance | 100 mL/min | 57 mL/min | 141 mL/min | 67.7 mL/min |
| Typical dosing for susceptible infections | 7.5 mg/kg 12/12 h | 1 mg/kg 8/8 h | 1 mg/kg 8/8 h | 1000 mg 12/12 h |

$F_{up}$: fraction unbound in plasma; $T_{1/2}$: half-life; $V_c$: central volume of distribution.

In this work, data was collected from inpatients receiving intravenous antibiotic therapy with amikacin, gentamicin, tobramycin, or vancomycin (chemical structures are presented in Figure 1 and some properties are summarized in Table 1), and their creatine clearance was estimated using five

equations plus seven variations of the Cockcroft-Gault formula (total of 12 different estimations). A direct measurement of GFR was not available, a limitation that prevented the comparison between observed and estimated clearance. The aim of this study was to evaluate the differences in estimated creatinine clearance produced by different equations and the influence of some patients' characteristics in these estimations, to better understand the impact of the choice of estimation method.

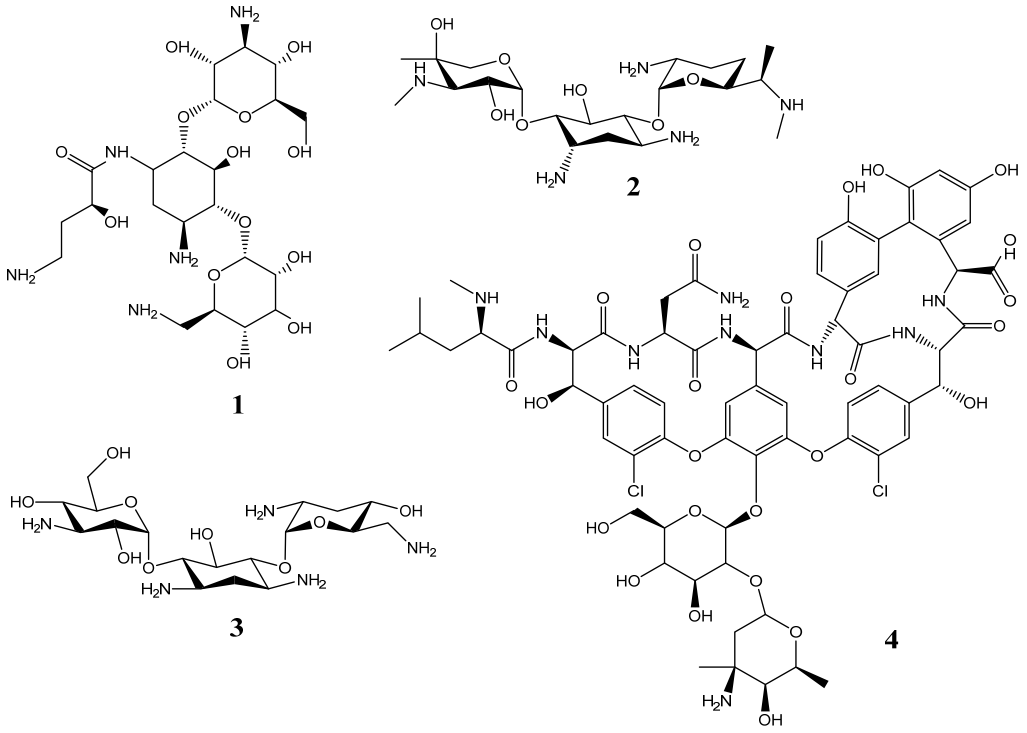


**Figure 1.** Chemical structure of amikacin (1), gentamicin (2), tobramycin (3) and vancomycin (4).

## 2. Materials and methods

### *2.1. Patients and methods*

Data was gathered from 82 inpatients receiving antibiotic therapy for the treatment of serious infections of different etiologies with intravenous amikacin, gentamicin, tobramycin, or vancomycin in CHUP (*Centro Hospitalar Universitário do Porto*). This information included demographics, such as biological sex, age, total body weight, and height, as well as creatinine (enzymatic method) and drug plasma concentrations determined in multiple days throughout the treatment. All the collected creatinine concentrations were included in this study, in a total of 374 measurements. A summary of all collected data is presented in Table 2.

Creatinine clearance ($CL_{Cr}$) was estimated, in mL/min, according to Eqs (2) through (7). Seven adaptations of the Cockcroft-Gault (CG) equation were included, incorporating body weight as actual (TBW), ideal (IBW), adjusted (AdjBW), modified-adjusted (mAdjBW), and lean body weight (LBW), as described in Eqs (8) through (12). Additionally, variations of ideal plus a fixed percentage of 30, 40, or 50% were calculated. In these equations, body weight is in kg, H is height in m, age is in years, and SCr is the measured serum creatinine in mg/dL. BSA is the body surface area in $m^2$, calculated

according to the DuBois formula (1) [11] (height in cm).

$$\mathrm{BSA} = 0.007184 \times TBW^{0.425} \times H^{0.725} \tag{1}$$

Cockcroft-Gault (CG) Eq (2) must be multiplied by 0.85 for female individuals [12].

$$\mathrm{CL_{Cr}} = \frac{(140 - \mathrm{Age}) \times \mathrm{BW}}{\mathrm{SCr} \times 72} \tag{2}$$

Jelliffe [13] developed Eq (3), that can be normalized considering BSA Eq (4). Both equations should be multiplied by 0.9 for female individuals.

$$\mathrm{CL_{Cr}} = \frac{98 - [0.8 \times (\mathrm{Age} - 20)]}{\mathrm{SCr}} \tag{3}$$

$$\mathrm{CL_{Cr}} = \frac{(98 - [0.8 \times (\mathrm{Age} - 20)]) \times \left(\frac{\mathrm{BSA}}{1.73}\right)}{\mathrm{SCr}} \tag{4}$$

Wright equation (5) [14] is likewise multiplied by 0.77 for female individuals:

$$\mathrm{CL_{Cr}} = \frac{(6230 - 32.8 \times \mathrm{Age}) \times \mathrm{BSA}}{\mathrm{SCr} \times 88.42} \tag{5}$$

Corcoran–Salazar (CS) [15] also developed equations to estimate clearance. For male individuals, Eq (6) should be used, while for female individuals, Eq (7) is applied:

$$\mathrm{CL_{Cr}} = \frac{(137 - \mathrm{Age}) \times (0.285 \times \mathrm{TBW} + 12.1 \times \mathrm{H}^2)}{\mathrm{SCr} \times 51} \tag{6}$$

$$\mathrm{CL_{Cr}} = \frac{(146 - \mathrm{Age}) \times (0.287 \times \mathrm{TBW} + 9.74 \times \mathrm{H}^2)}{\mathrm{SCr} \times 60} \tag{7}$$

Ideal body weight was calculated using the Devine equation (8) [16]:

$$\mathrm{IBW} = 50 + 2.3 \times \left(\frac{\mathrm{H}}{2.54} - 60\right) \tag{8}$$

where height (H) is in centimeters and the factor 50 is replaced by 45.5 in female individuals. The adjusted body weight was calculated as Eq (9) [18] and modified adjusted body weight as Eq (10) [17]:

$$\mathrm{AdjBW} = \mathrm{IDW} + 0.4 \times (\mathrm{TBW} - \mathrm{IBW}) \tag{9}$$

$$\mathrm{mAdjBW} = \mathrm{mIBW} + 0.4 \times (\mathrm{TBW} - \mathrm{mIBW}) \tag{10}$$

Lean body weight for male individuals was calculated as Eq (11) for males and as Eq (12) for females [19]:

$$\mathrm{LBW} = \frac{9270 \times \mathrm{TBW}}{6680 + 216 \times \mathrm{BMI}} \tag{11}$$

$$\mathrm{LBW} = \frac{9270 \times \mathrm{TBW}}{8780 + 244 \times \mathrm{BMI}} \tag{12}$$

**Table 2.** Summary of collected clinical data, with the indication of lower and upper limits and calculation of average value for each parameter.

| | Full database | Amikacin | Gentamicin | Tobramycin | Vancomycin |
|---|---|---|---|---|---|
| Biological sex | F: 34 (41.5%)<br>M: 48 (58.5%) | F: 1; M: 7 | F: 8; M: 14 | F: 4; M: 1 | F: 21; M: 26 |
| Age (years) | 7–93<br>(avg 58) | 14–87<br>(avg 57) | 7–88<br>(avg 58) | 13–19<br>(avg 15) | 19–93<br>(avg 63) |
| Weight (kg) | 15.5–140<br>(avg 66.2) | 50.0–92.5<br>(avg 66.0) | 15.5–85.0<br>(avg 66.0) | 25.8–44.5<br>(avg 33.0) | 44.5–121.0<br>(avg 70) |
| Height (cm) | 108–185<br>(avg 164.7) | 163–180<br>(avg 169) | 108–185<br>(avg 165) | 130–158<br>(avg 146) | 147–180<br>(avg 166) |
| [Cr] (mg/dL) | 0.63–4.78<br>(avg 0.93) | 0.47–1.58<br>(avg 0.93) | 0.29–1.89<br>(avg 0.83) | 0.35–0.64<br>(avg 0.49) | 0.27–4.78<br>(avg 1.02) |
| $C_{min}$ (mg/L) | --- | 0.30–16.40<br>(avg 3.70) | 0.20–4.80<br>(avg 1.05) | 0.06–0.23<br>(avg 0.17) | 4.50–45.60<br>(avg 16.45) |
| $C_{max}$ (mg/L) | --- | 19.70–87.80<br>(avg 38.97) | 2.90–19.50<br>(avg 9.22) | 16.32–36.12<br>(avg 27.05) | 11.20–60.10<br>(avg 25.99) |

F: females; M: males; avg: average value; [Cr]: serum creatinine concentration; $C_{min}$: antibiotic concentration measured right before a dose; $C_{max}$: antibiotic concentration measured 1 h (aminoglycosides amikacin, gentamicin and tobramycin) or 3 h (vancomycin) after the beginning of an infusion.

### *2.2. Data analysis*

Patients were stratified into four groups according to body composition, using body mass index (BMI) as an indicator: underweight (BMI < 17.9 kg/m$^2$), normal weight (BMI = 18–24.9 kg/m$^2$), overweight (BMI = 25–29.9 kg/m$^2$), and obese (BMI ≥ 30 kg/m$^2$). Data was also analyzed according to the sex and age of the patients, as well as to their measured serum creatinine concentration.

BMI was calculated as Eq (13), where TBW is total body weight in kg and H is height in m:

$$\mathrm{BMI} = \frac{\mathrm{TBW}}{\mathrm{H}^2} \tag{13}$$

Calculations of estimated $CL_{Cr}$ values were performed in Microsoft Excel 365. Plots were also generated in Excel. The number of records of creatinine concentration of each group is indicated in every plot (as *n*).

## 3. Results and discussion

All the serum creatinine concentrations collected from the patients in the study population were included in this study. The distribution of this data is presented in Figure 2.

Analyzing the distribution of creatinine serum concentrations (SCr), it is noticeable that men of the population studied in this work had higher SCr, as expected. Patients with normal BMI reached more extreme values (mainly elevated) of SCr comparing to the other body composition groups. With increasing age, SCr was also increased, predominantly in patients older than 70 years old.

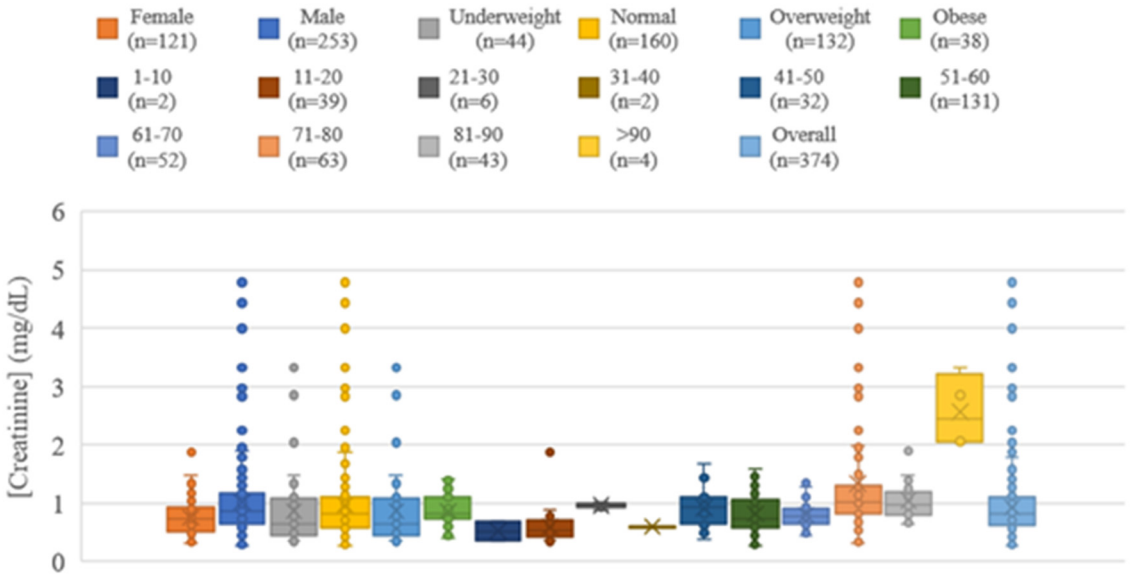


**Figure 2.** Distribution of measured creatinine serum concentrations in different groups (biological sex, body composition and age) and of all measures included in this study (overall).

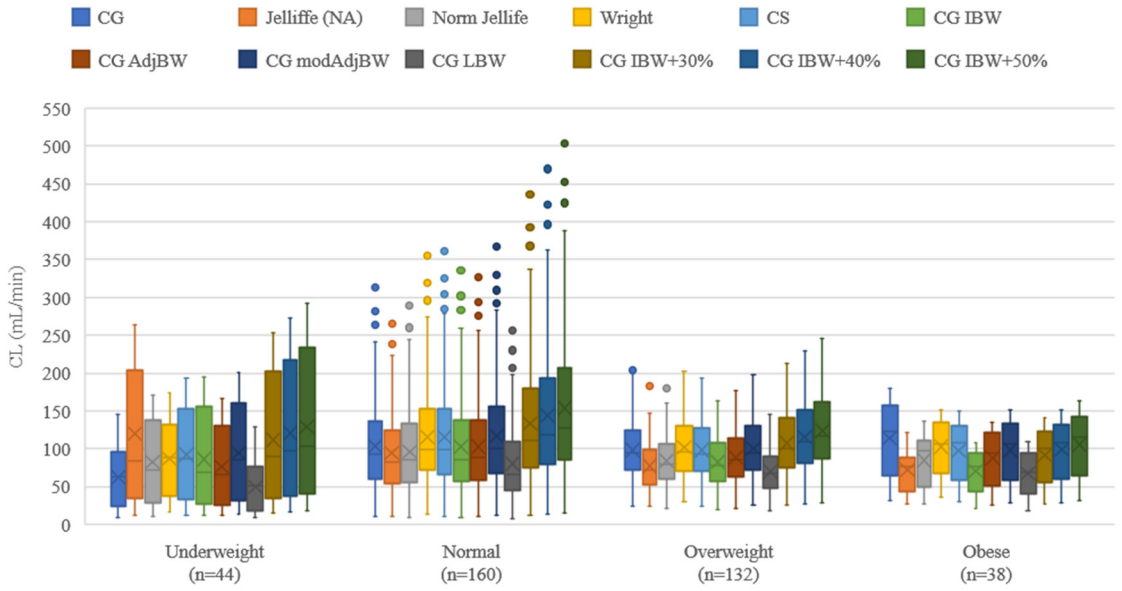


**Figure 3.** Distribution of clearance estimations according to body type (based on BMI).

Patients were then grouped according to their body composition based on BMI. The estimations of $CL_{Cr}$ based on this stratification are presented in Figure 3. In the studied population, there was more variability in the estimated $CL_{Cr}$ within the normal weight group. Furthermore, data from this group, followed by the underweight group, resulted in higher estimated $CL_{Cr}$. However, it is important to note that only patients under 20 years old and older than 71 years old were part of the underweight group.

Overweight and obese patients had lower and less varying estimated CLCr.

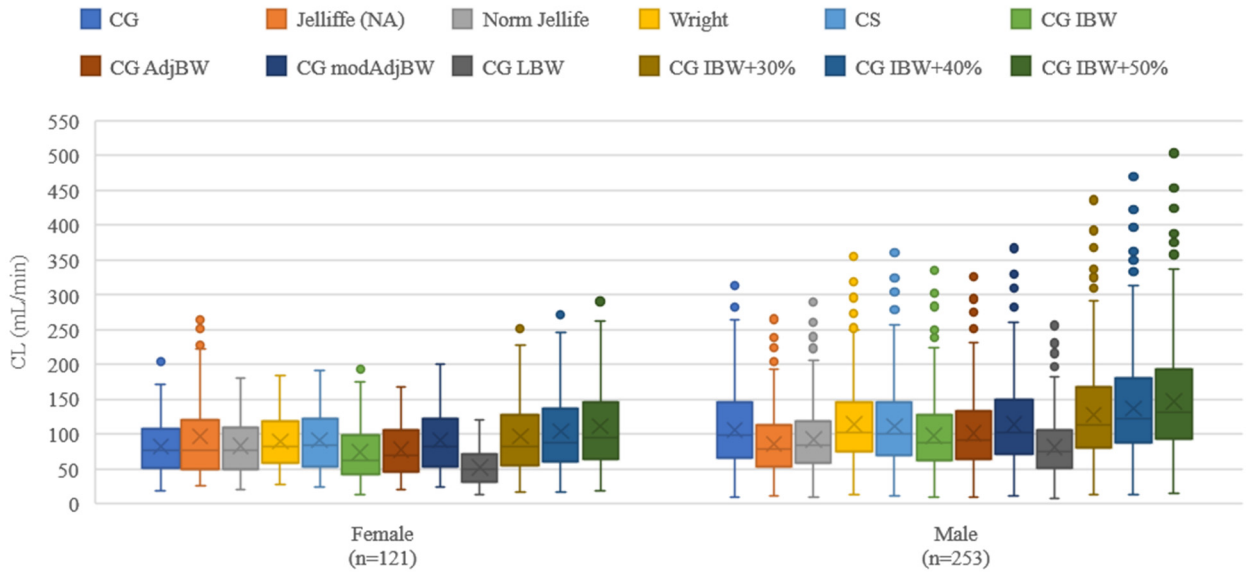


**Figure 4.** Distribution of clearance estimations according to biological sex.

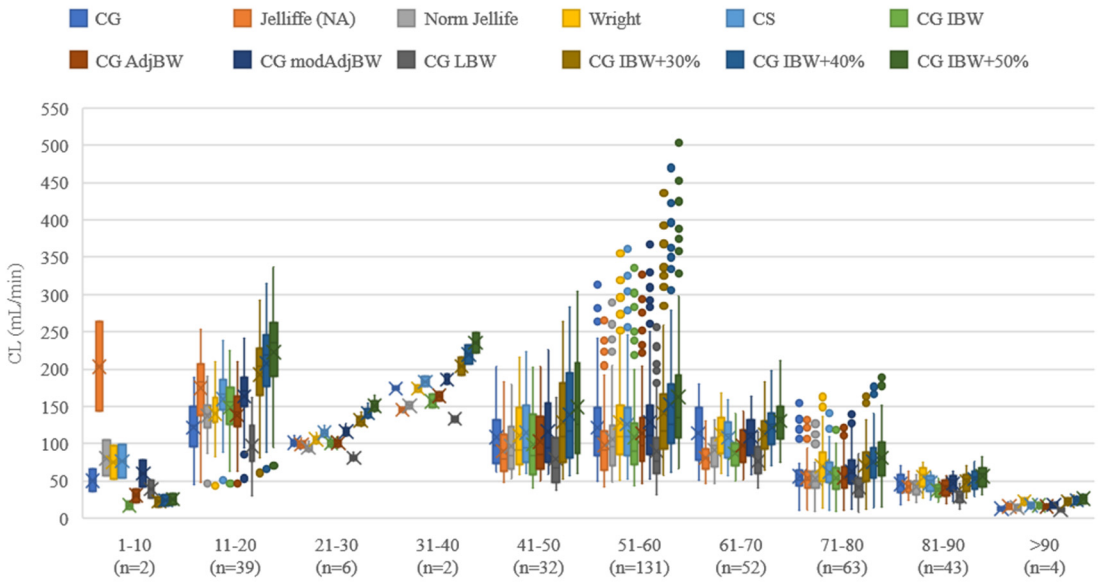


**Figure 5.** Distribution of clearance estimations according to age.

Regarding biological sex, the data from male individuals on populations analyzed in this study resulted in higher estimated $CL_{Cr}$ (Figure 4), in agreement with expected.

Figure 5 presents the distribution of results considering the age group of the patients. In the age group 1–10, there are only 2 data entries, corresponding to the same patient, an underweight 7-year-old female (TBW = 15.5 kg, H = 108 cm). Since the nonadjusted Jelliffe equation only takes into consideration age and does not include any body composition parameters, this data significantly

deviates from the remaining estimations. The estimated $CL_{Cr}$ decreased with age. The most considerable variations were observed in patients between 51 and 60 years old and were less perceptible above 80 years old.

Next, each body composition group was stratified for age groups. Results are presented in Figures 6–9. Consistently throughout every BMI group, there was less variability in patients older than 61 years. The estimation using the Cockcroft-Gault equation considering lean body weight (CG LBW) results in lower estimated $CL_{Cr}$.

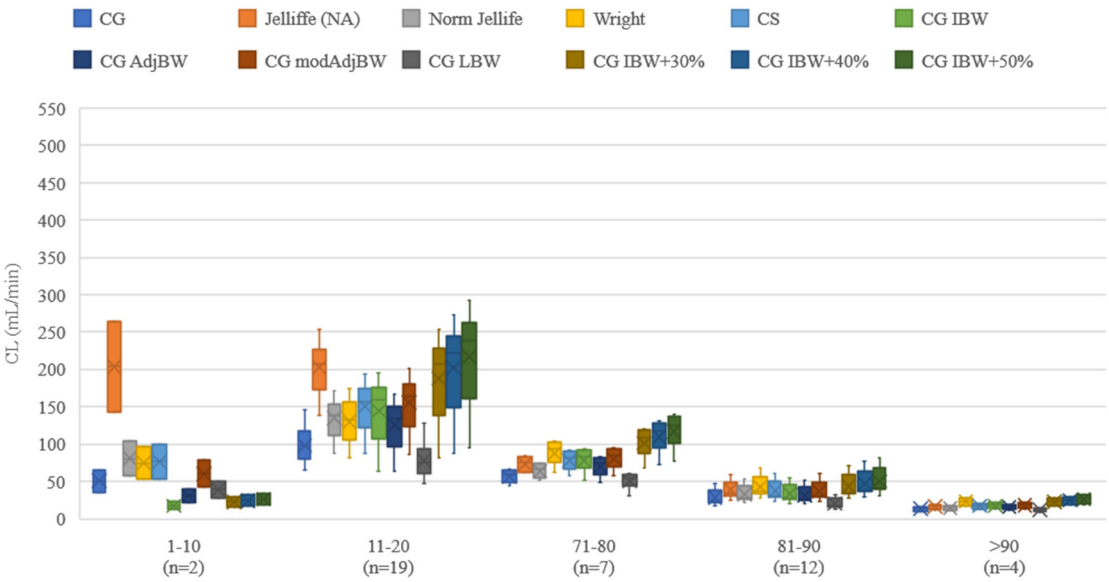


**Figure 6.** Distribution of clearance estimations according to age for underweight patients.

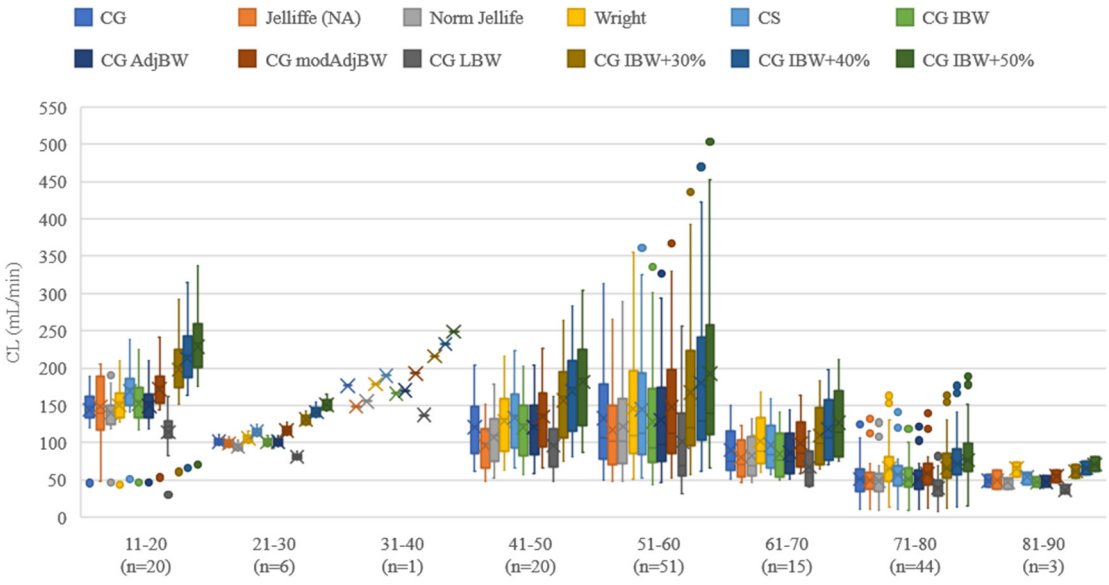


**Figure 7.** Distribution of clearance estimations according to age for patients with normal BMI.

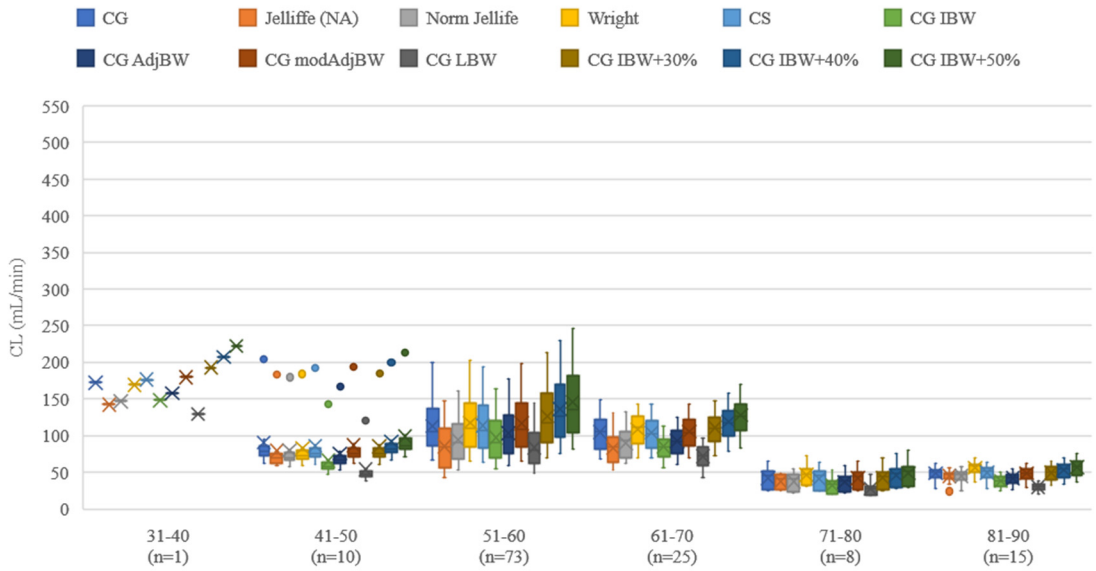


**Figure 8.** Distribution of clearance estimations according to age for overweight patients.

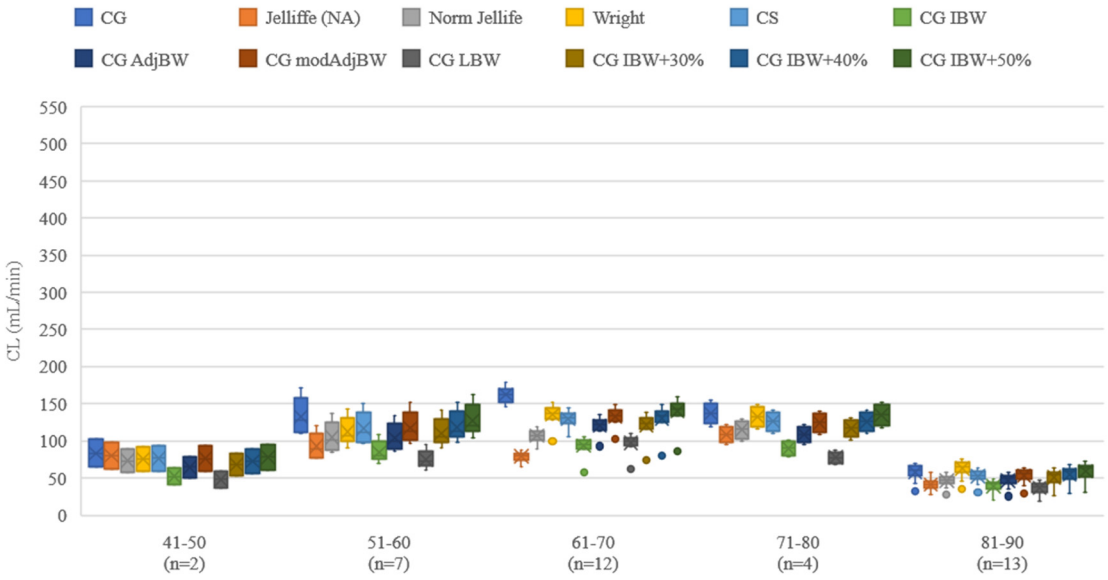


**Figure 9.** Distribution of clearance estimations according to age for obese patients.

The measured serum creatinine concentration was also analyzed, and this data is presented in Figure 10. Patients with serum creatinine concentration below reference criteria had an ampler range of estimated CLCr.

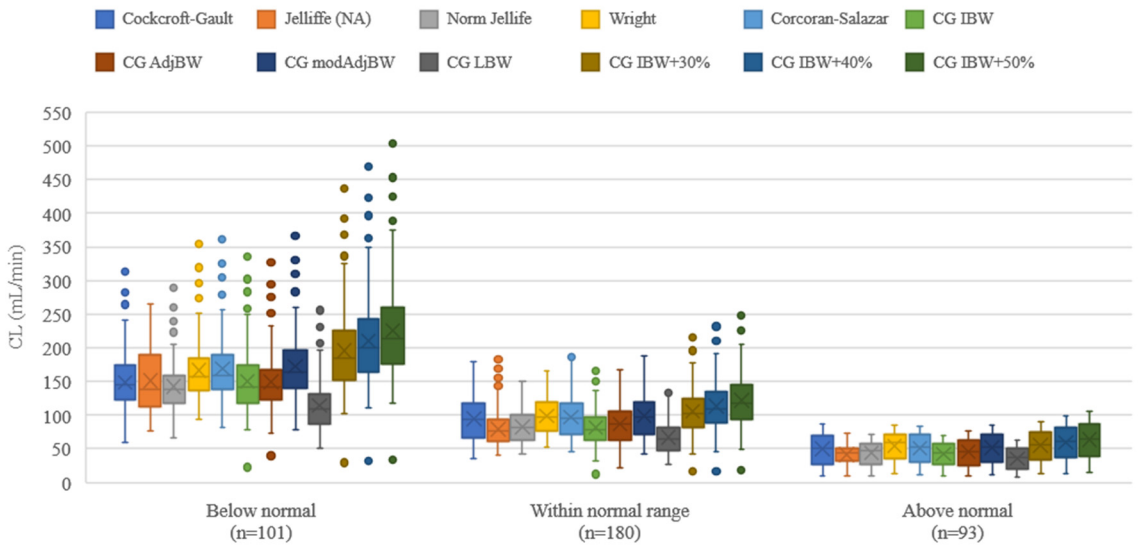


**Figure 10.** Distribution of clearance estimations according to measured serum creatinine concentration (CHUP reference: normal range of [Cr] is 0.7–1.2 mg/dL for male patients and 0.5–0.9 mg/dL for female patients).

## 4. Conclusions

Renal function can be a crucial factor to consider when adjusting therapeutic regimens of inpatients (whose kidneys can suffer significant deterioration throughout treatment duration). Since the most accurate indicator GFR is not as easily determined, creatinine serum concentration is more often used to estimate renal clearance, using various equations. As there is no standard estimation method, estimated creatinine clearance can be significantly disparate, which will influence therapeutic regimens adjustment.

Analyzing the influence of the different clearance estimation equations, the estimation using the Cockcroft-Gault equation considering lean body weight (CG LBW) produced lower estimated $CL_{Cr}$ in almost all groups. Since creatinine is a product of natural muscle breakdown, this observation can indicate an overestimation of $CL_{Cr}$ when using other components of body composition.

With this retrospective study, the differences between creatinine clearance estimation equations and the impact of the variables entered in these calculations were highlighted. These results supplement the knowledge about creatinine clearance estimation and provide insight on the disparities of the available estimation methods, that can help clinicians make a better informed and tailored decision when choosing how to evaluate a patient's renal function.

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## Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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