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Estimation of glomerular filtration rate in hospitalised patients : are we overestimating renal function ?

THESE

préparée sous la direction du Professeur Michel Burnier
avec la co-direction du Professeur Luca Gabutti

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Résumé

Estimer la filtration glomérulaire chez les personnes âgées, tout en tenant compte de la difficulté supplémentaire d'évaluer leur masse musculaire, est difficile et particulièrement important pour la prescription de médicaments. Le taux plasmatique de la créatinine dépend à la fois de la fraction d'élimination rénale et extra-rénale et de la masse musculaire. Actuellement, pour estimer la filtration glomérulaire différentes formules sont utilisées, qui se fondent principalement sur la valeur de la créatinine. Néanmoins, en raison de la fraction éliminée par les voies tubulaires et intestinales la clairance de la créatinine surestime généralement le taux de filtration glomérulaire (GFR).

Le but de cette étude est de vérifier la fiabilité de certains marqueurs et algorithmes de la fonction rénale actuellement utilisés et d'évaluer l'avantage additionnel de prendre en considération la masse musculaire mesurée par la bio-impédance dans une population âgée (> 70 ans) et avec une fonction rénale chronique compromise basée sur MDRD eGFR (CKD stades III-IV). Dans cette étude, nous comparons 5 équations développées pour estimer la fonction rénale et basées respectivement sur la créatinine sérique (Cockcroft et MDRD), la cystatine C (Larsson), la créatinine combinée à la bêta-trace protéine (White), et la créatinine ajustée à la masse musculaire obtenue par analyse de la bio-impédance (MacDonald). La bio-impédance est une méthode couramment utilisée pour estimer la composition corporelle basée sur l'étude des propriétés électriques passives et de la géométrie des tissus biologiques. Cela permet d'estimer les volumes relatifs des différents tissus ou des fluides dans le corps, comme par exemple l'eau corporelle totale, la masse musculaire (=masse maigre) et la masse grasse corporelle.

Nous avons évalué, dans une population âgée d'un service interne, et en utilisant la clairance de l'inuline (single shot) comme le « gold standard », les algorithmes de Cockcroft (GFR CKC), MDRD, Larsson (cystatine C, GFR CYS), White (beta trace protein, GFR BTP) et Macdonald (GFR = ALM, la masse musculaire par bio-impédance.

Les résultats ont montré que le GFR (mean ± SD) mesurée avec l'inuline et calculée avec les algorithmes étaient respectivement de : 34.9±20 ml/min pour l'inuline, 46.7±18.5 ml/min pour CKC, 47.2±23 ml/min pour CYS, 54.4±18.2ml/min pour BTP, 49±15.9 ml/min pour MDRD et 32.9±27.2ml/min pour ALM. Les courbes ROC comparant la sensibilité et la spécificité, l'aire sous la courbe (AUC) et l'intervalle de confiance 95% étaient respectivement de : CKC 0.68 (055-0.81), MDRD 0.76 (0.64-0.87), Cystatin C 0.82 (0.72-0.92), BTP 0.75 (0.63-0.87), ALM 0.65 (0.52-0.78).

En conclusion, les algorithmes comparés dans cette étude surestiment la GFR dans la population âgée et hospitalisée, avec des polymorbidités et une classe CKD III-IV. L'utilisation de l'impédance bioélectrique pour réduire l'erreur de l'estimation du GFR basé sur la créatinine n'a fourni aucune contribution significative, au contraire, elle a montré de moins bons résultats en comparaison aux autres équations. En fait dans cette étude 75% des patients ont changé leur classification CKD avec MacDonald (créatinine et masse musculaire), contre 49% avec CYS (cystatine C), 56% avec MDRD, 52% avec Cockcroft et 65% avec BTP. Les meilleurs résultats ont été obtenus avec Larsson (CYS C) et la formule de Cockcroft.

Estimation of glomerular filtration rate in hospitalised patients: are we overestimating renal function?

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Summary

QUESTIONS UNDER STUDY AND PRINCIPLES: Estimating glomerular filtration rate (GFR) in hospitalised patients with chronic kidney disease (CKD) is important for drug prescription but it remains a difficult task. The purpose of this study was to investigate the reliability of selected algorithms based on serum creatinine, cystatin C and beta-trace protein to estimate GFR and the potential added advantage of measuring muscle mass by bioimpedance.

METHODS: In a prospective unselected group of patients hospitalised in a general internal medicine ward with CKD, GFR was evaluated using inulin clearance as the gold standard and the algorithms of Cockcroft, MDRD, Larsson (cystatin C), White (beta-trace) and MacDonald (creatinine and muscle mass by bioimpedance).

RESULTS: 69 patients were included in the study. Median age (interquartile range) was 80 years (73–83); weight 74.7 kg (67.0–85.6), appendicular lean mass 19.1 kg (14.9–22.3), serum creatinine 126 μmol/l (100–149), cystatin C 1.45 mg/l (1.19–1.90), beta-trace protein 1.17 mg/l (0.99–1.53) and GFR measured by inulin 30.9 ml/min (22.0–43.3). The errors in the estimation of GFR and the area under the ROC curves (95% confidence interval) relative to inulin were respectively: Cockcroft 14.3 ml/min (5.55–23.2) and 0.68 (0.55–0.81), MDRD 16.3 ml/min (6.4–27.5) and 0.76 (0.64–0.87), Larsson 12.8 ml/min (4.50–25.3) and 0.82 (0.72–0.92), White 17.6 ml/min (11.5–31.5) and 0.75 (0.63–0.87), MacDonald 32.2 ml/min (13.9–45.4) and 0.65 (0.52–0.78).

CONCLUSIONS: Currently used algorithms overestimate GFR in hospitalised patients with CKD. As a consequence eGFR targeted prescriptions of renal-cleared drugs, might expose patients to overdosing. The best results were obtained with the Larsson algorithm. The determination of muscle mass by bioimpedance did not provide significant contributions.

Key words: glomerular filtration rate; eGFR; estimation; bioimpedance; inulin clearance; cystatin C; beta-trace protein; inpatients

Introduction

Glomerular filtration rate (GFR) can be measured using standardised methods such as the determination of inulin clearance or by calculating the clearance of alternative substrates, such as iodinated contrast agents (for instance, iohexol) or radioisotopes [1]. In clinical practice, however, determination of GFR by these methods is so cumbersome and costly that clinicians cannot use them on a regular basis and must be satisfied with an estimation of GFR calculated from endogenous markers of kidney function, traditionally serum creatinine and, more recently, cystatin C and beta-trace protein. The determination of creatinine is reproducible, not expensive and easily accessible. However, the use of creatinine for measuring kidney function has a number of limitations, specifically owing to the fraction of the substance eliminated by non-renal routes and to its dependence on muscle mass and, last but not least, on dietary intake [2–11]. Cystatin C and beta-trace protein do offer some theoretical advantages, the main one being their low susceptibility to anthropometric variables [12–20]; however, they have failed to win a place in the delicate compromise between determination cost, accuracy and reproducibility despite the fact that they have now been available for a number of years [21–24]. Also owing to limited intra-individual variability, creatinine thus continues to be the endogenous substrate of first choice for estimating kidney function and, when appropriate, for determining the stage of dysfunction [25, 26].

Starting from creatinine it is possible to estimate either, GFR by a number of formulas, the most popular of which is the one obtained by Levey in 1999 from the Modification of Diet in Renal Disease (MDRD) study data [4, 5] or creatinine clearance with the equation published by Cockcroft in 1976 [3]. Because of the fraction eliminated by tubular and intestinal routes, creatinine clearance usually overestimates GFR; however, the difference between the two measurements falls within determination-related error dispersion [27]. For the purpose of correcting the error given by the difference between individual muscle mass and average muscle mass by age group [28, 29], MacDonald pro-

posed in 2006 an equation that also included determination of appendicular lean mass by bioelectrical impedance analysis [30, 31].

There are also dedicated equations available for estimating GFR from cystatin C and beta-trace protein (proposed by Larsson in 2004 [13] and by White in 2007, respectively [20]), that are not or little affected by body composition [12–20] but are unfortunately exposed to great intra- and inter-individual variability just like the substrates they are based on [21–24].

Despite progress in knowledge about endogenous markers of kidney function, the determination of GFR remains difficult. The difficulty is further enhanced in patients at the extremes of the normal distribution, particularly with regard to weight, muscle mass, and age [2, 7, 32].

The frail elderly who are admitted to internal medicine wards, with their many comorbidities and the consequences of their disabilities, often have complex conditions treated with medications having a narrow therapeutic spectrum and, by definition, they put the equations used for estimating kidney function to the hardest of tests. This is even more so when we know that one third to one fourth of all patients above 60 years of age, some of whom with normal creatinine values, have at least stage III chronic kidney disease (CKD) [33] and that GFR has been shown to decrease by 0.8 ml/min/year on average, starting from the age of 40 [2].

Confused by the number and diversity of available equations, and anxious to verify their accuracy in the elderly population of our internal medicine wards with CKD and moderately compromised kidney function, we decided to compare the main equations (Cockcroft [3], MDRD [5], White [20], Larsson [13] and MacDonald [30]), using inulin clearance as the gold standard [34, 35].

Materials and methods

Patients and measurements

We recruited 70 unselected Caucasian patients with CKD and moderate kidney function impairment (stage III–IV according to KDOQI guidelines [25]) among the elderly population (>70 year old) of the internal medicine wards of two secondary care hospitals in the south of Switzerland (Regional Hospitals of Locarno and Bellinzona). Every patient had to be cardiopulmonary compensated showing a stable weight at least in the 4 days before inclusion. We excluded patients with evidence of unstable renal function in the last two weeks (serum creatinine excursions >20 µmol/l), before inclusion.

To minimise bias, starting on kick-off day, all patients meeting the selection criteria were asked to participate in the study and every patient from whom an informed consent was obtained was recruited.

On the inclusion day, blood samples were obtained from each patient to determine serum creatinine, cystatin C and beta-trace protein additionally bioimpedance was assessed. On the same day the glomerular filtration rate (GFR) was measured using a single bolus inulin clearance [36].

Blood samples were rapidly (waiting time <15 minutes) centrifuged for 10 minutes (1,500 RPM) in the local labor-

atory. Plasma and serum were extracted and frozen at respectively –80 and –20 °C and then sent to the "Central Chemical and Immunology Laboratory of the Public Hospital Network of Bellinzona" to determine the serum creatinine, Cystatin C and beta-trace protein and to the "Nephrology Research Laboratory of the Lausanne University Hospital" to determine the plasma inulin.

Laboratory assessments for serum creatinine, cystatin C and beta-trace protein and for plasma inulin

To obtain the serum creatinine value, a modified IDMS calibrated kinetic Jaffé reaction on a Hitachi 912 photometer was used. Serum cystatin C and beta trace-protein levels were analysed with the Siemens method using the Behring Nephelometer II.
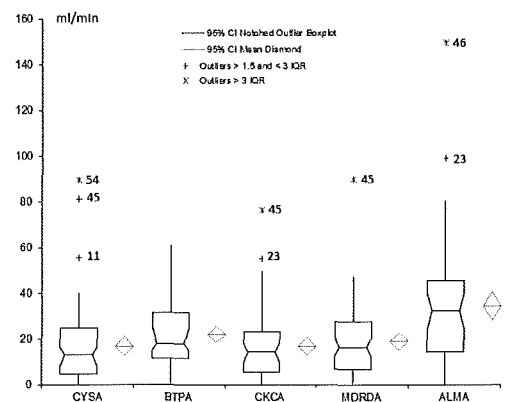

Figure 1

Box Plot showing the absolute error in estimating GFR (inulin clearence as the gold standard). CYSA, BTPA, CKCA, MDRDA, ALMA = absolute error in estimating the GFR using algorithms based respectively on Cystatin C; Beta-trace protein, creatinine and anthropometric values (Cockcroft); creatinine and anthropometric values (MDRD), creatinine, anthropometric values and appendicular lean mass (approximating muscle mass) measured by bioimpedance.
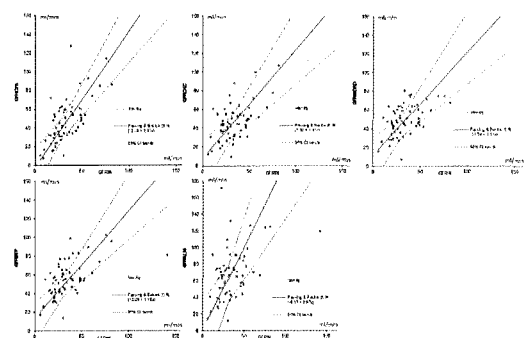

Figure 2

Scatterplots comparing the estimations obtained with the tested algorithms to the GFR measured by inulin; the diagonal line indicates the equality. A Passing and Bablok analysis shows the trend of the distribution and its 95% confidence intervals. GFR CYS = GFR estimated by Cystatin C; GFR BTP = GFR estimated by Beta Trace Protein; GFR ALM = GFR estimated by Appendicular Lean Mass and creatinine. GFR CKC= GFR estimated by Cockcroft's algorithm. GFR MDRD = GFR estimated by MDRD (Modification of Diet in Renal Disease) algorithm.

Plasma inulin was determined using a spectrophotometer (microadaptation of an anthrone procedure on a Technicon Autoanalyser [37]).

Inulin clearance

Inulin clearance has been used as the gold standard for the determination of GFR [39, 40]. Considering (1.) the known good correlation between the clearance values obtained with a constant infusion of inulin and with a single shot method respectively and (2.) the simplicity of the short infusion strategy, the latter was used to determine the GFR [35, 36].

Two timed blood samples after the bolus injection of inulin could have been enough to calculate the GFR [36]; we decided however to increase the number of blood samples to 4 in order to set up a better disappearance curve and to estimate the inulin clearance (one-compartment model) thrice for every patient according to the following formula.

$$GFR \ Inulin = (ln \ C_{n-1} - ln \ C_n)/(t_{n-1} - t_n)$$
$$(C = \text{inulin concentration [mg/l]; t = time [min]})$$

Concerning the inulin administration; on the study day, at time 0, a bolus of 12.5 ml of Inutest® (a solution containing 25% inulin) was administered intravenously over 10 minutes. Altogether five blood samples were obtained; the first one prior to inulin administration and then at 90, 180, 270 and 360 minutes.

GFR and creatinine clearance estimation

To estimate creatinine clearance and GFR, the algorithms of Cockcroft (CCL CKC) and Levey (GFR MDRD) based on serum creatinine and anthropometric values, Larsson based on cystatin C (GFR CYS), White based on serum

Figure 3

ROC Curves plotting the sensitivity against 1 minus the specificity of the selected algorithms in predicting an inulin clearance <30 ml/min.
CYS = GFR estimated by Cystatin C; BTP = GFR estimated by Beta Trace Protein; ALM = GFR estimated by Appendicular Lean Mass and creatinine. CKC= GFR estimated by Cockcroft's algorithm. MDRD = GFR estimated by MDRD (Modification of Diet in Renal Disease) algorithm. The ideal test would have an AUC of 1, whereas a random guess would have an AUC of 0.5.

creatinine and beta-trace protein (GFR BTP) and MacDonald based on serum creatinine, anthropometric values and the appendicular lean mass obtained by bio-impedance (proportional to muscular mass) (GFR ALM) were used (table 1).

Cystatin C and Beta Trace Protein

Cystatin C is an endogenous, 13 kilo-Dalton protein, generated at a relatively constant rate, freely filtered by the glomeruli and reabsorbed and catabolised by the tubular epithelial cells [12, 13].

Similarly, Beta Trace Protein is a low molecular weight glycoprotein, primarily isolated as prostaglandin D2 synthase, in its turn filtered by the glomeruli and with minimal extra-renal elimination [19, 20].

Predicting appendicular lean mass by bioimpedance

The appendicular lean mass was estimated by bioimpedance; a commonly used method for estimating body composition based on the study of the passive electrical properties of the biological tissues. Bio-impedance allows estimating the relative volumes of different tissues or fluids in the body as total body water, appendicular lean mass (approximating the muscle mass) and fat body weight.

The efficacy and the reproducibility of the bioimpedance in estimating the body composition has been evaluated and judged favorably in many studies [38–40].

To perform the measurements electrodes were put on the dorsal surfaces of the ipsilateral wrist and ankle (on the metacarpal- and metatarsal phalangeal joint of the hand and foot) and a BIA 101 device (Akern, Florence, Italy) was used. Then, on the basis of the resulting resistance (Rz) and reactance (Xc), using the Bodygram® software, the appendicular lean mass (ALM) was calculated.

Statistical and data analysis

Statistical and data analysis were performed using the SPSS 20.0 and the Analyse-it 2.26 statistical software packages. Considering that the absolute error in predicting GFR is not normally distributed we decided to analyse the significance using a Friedman Test. In all cases a p ≤0.05 was considered statistically significant. Distributions were graphically depicted using box-plots and scatterplots.

The quality of the measurements of the inulin clearances was assessed analysing the intra-patient dispersion of the GFR values calculated as the median of the difference between the extremes.

To compare the accuracy of the selected prediction algorithms we used: a Bland and Altman analysis in which the error is plotted against the mean of measured and estimated GFR [41], a Passing and Bablok analysis depicting graphycally the trend and 95% confidence intervals of the distribution and receiver operating characteristic curves (ROC) which give a graphical display of sensitivity and specificity of the test. In ROC curves the sensitivity is plotted versus 1 – specificity, with each point of the curve representing a different cut-off level. The area under the curve (AUC) describes the test overall performance; to facilitate comparisons between individual variables the value was given with the 95% confidence interval.
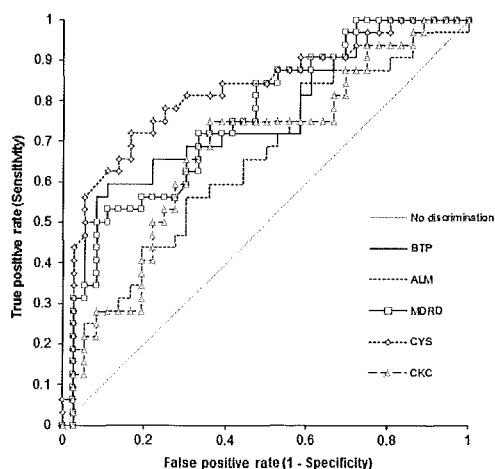
Ethical approval was obtained from the local Ethics Committee (Comitato Etico Cantonale, Bellinzona), and all participants gave written informed consent prior to enrolment.

Results

From the 70 recruited patients, one was excluded for incomplete blood samples.

The demographic and clinical characteristics of the study group are presented in table 2. As a comparison, the mean age and eGFR (MDRD) of the totality of the patients admitted to the internal medicine wards of the two hospitals in the study year (N = 5,676) was (median and interquartile range) 76 (66–84) years and 57 (38–81) ml/min respectively. Patients with chronic kidney disease stage III–IV represented 52.9% of the entire population.
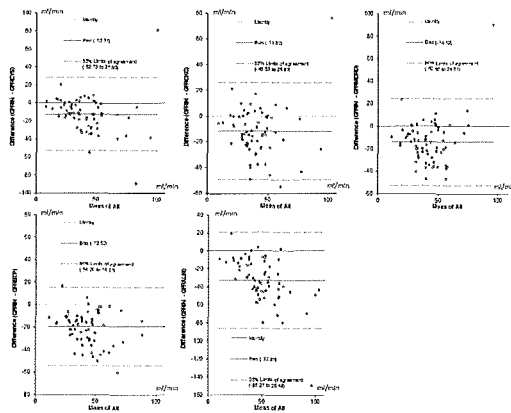
The GFR measured with inulin and calculated with the selected algorithms and the absolute error in performing the estimation (median and mean values to allow a quantitative comparison) are listed in table 3. The reliability of the inulin clearance was assessed analysing the intra-patient absolute difference between the extremes of the three individual determinations (median, 25% and 75% interquartile ranges which were: 8.2, 3.6 and 13.6 ml/min respectively). All selected algorithms significantly overestimate GFR in our group of patients (p <0.001).

The absolute error in estimating GFR is depicted graphically in figure 1. The difference among the median values of the selected algorithms was found to be significant (p <0.001). The estimations obtained on the basis of cystatin C were characterised by the lowest median and mean error (table 3), while those obtained with the McDonald algorithm were the worst. Outliers 45 and 46 were characterised by a large body weight and estimated muscular mass (118 and 98, and 40 and 35 kg respectively).

The distribution of the values obtained estimating GFR with the 5 tested algorithms, compared to the reference method (inulin clearance) is depicted graphically using scatterplots in figure 2. A Passing and Bablok analysis shows the trend of the distribution and its 95% confidence intervals compared to the identity line.

The ROC curves comparing sensitivity and specificity of the tested algorithms in predicting an inulin clearance <30 ml/min are depicted in figure 3. The area under the curves and the 95% confidence intervals were respectively: CKC 0.68 (0.55–0.81), MDRD 0.76 (0.64–0.87), Cystatin C 0.82 (0.72–0.92), BTP 0.75 (0.63–0.87), ALM 0.65 (0.52–0.78). The Bland and Altman analysis is shown in figure 4.

The percentage of patients wrongly attributed on the basis of the selected prediction algorithm, to a lower or a higher CKD stage is summarised in table 4. GFR CYS, inducing less class changes compared to the other algorithms, obtained the better score followed in order by GFR CKC, GFR MDRD, GFR BTP and GFR ALM.

Figure 4

Bland and Altman analysis. In this analysis the differences between the gold standard and the selected prediction algorithm, are plotted against the mean of measured and calculated GFR for each individual patient.
GFR CYS = GFR estimated by Cystatin C; GFR BTP = GFR estimated by Beta Trace Protein; GFR ALM = GFR estimated by Appendicular Lean Mass and creatinine. GFR CKC= GFR estimated by Cockcroft's algorithm. GFR MDRD = GFR estimated by MDRD (Modification of Diet in Renal Disease) algorithm.

Table 1: Selected estimation algorithms. Formula used to estimate the Creatinine Clearance and the GFR respectively.

GFR or CCl (ml/min)	Algorithm
CCL CKC	(140 − age [year]) × weight [kg] / (creatinine [µmol/l] × 72) × (0.85 if female)
GFR MDRD	$175 \times (\text{creatinine [µmol/l]})^{-1.154} \times (\text{age [year]})^{-0.203} \times (0.742 \text{ if female})$
GFR CYS	$77.239 \times \text{Cystatin C (mg/l)}^{-1.2623}$
GFR BTP	$167.8 \times \text{BTP [mg/l]}^{-0.758} \times \text{creatinine [µmol/l]}^{-0.204} \times (0.871 \text{ if female})$
GFR ALM	$10^{1.008-1.014 \times \text{LOG10 (creatinine [µmol/l] / 88)} + 0.01644 \times \text{ALM [kg]} + 0.07108 \times \sqrt{\text{weight (Kg)}}}$

CCL CKC = creatinine clearance estimated by the Cockcroft algorithm; GFR MDRD = GFR estimated by the MDRD (Modification of Diet in Renal Disease) algorithm; GFR CYS = GFR estimated on the basis of the cystatin C value; GFR BTP = GFR estimated on the basis of the creatinine and the beta-trace protein value; GFR ALM = GFR estimated on the basis of the creatinine and the appendicular lean mass.

Table 2: Clinical characteristics of the studied population (n = 69).

	Median (25–75% interquartile range)	Mean ± SD
Age (years)	80 (73–83)	78 ± 7
Weight (kg)	74.7 (67.0–85.6)	77.3 ± 15.2
BMI (kg/m^2)	26.0 (23.3–30.0)	27.3 ± 5.2
ALM (kg)	19.1 (14.9–22.3)	19.1 ± 6.1
Creatinine (µmol/l)	126 (100–149)	134 ± 62
Cystatin C (mg/l)	1.45 (1.19–1.90)	1.71 ± 0.87
Beta-trace protein (mg/l)	1.17 (0.99–1.53)	1.34 ± 0.64

Discussion

In this study, we compared 5 different equations designed to estimate kidney function, based on serum creatinine (Cockcroft [3] and MDRD [5]), cystatin C (Larsson [13]), creatinine combined with beta-trace protein (White [20]), and creatinine adjusted for muscle mass obtained by bio-electrical impedance analysis (MacDonald [30]), respectively. Inulin clearance measured by the single shot method was taken as the gold standard [34–36]. The population under study, entirely of European Caucasian ethnicity, was chosen amongst the inpatients admitted to the internal medicine wards of two secondary care hospitals in southern Switzerland. The only criteria for their selection were, an age of >70 years and a chronic compromised kidney function based on MDRD eGFR (CKD stages III–IV).

As suggested by previous studies [2, 32], all tested equations are on average significantly overestimating kidney function (+11.8 ml/min Cockcroft, +12.4 ml/min cystatin C, +14.1 ml/min MDRD, +19.5 ml/min beta-trace protein, +32.9 ml/min creatinine and muscle mass). In this respect, a considerable number of patients would have changed their KDOQI CKD severity classification by adjusting GFR for the results of inulin clearance: 49% in the estimation based on cystatin C, 56% by MDRD, 52% by Cockcroft, 65% by beta-trace protein and 75% by creatinine and muscle mass (table 4).

The inaccuracy of equations in this inpatient population with extreme characteristics related to old age and polymorbidity is not surprising and has been previously reported [32].

However, considering how some criticalities attributed to creatinine relate to the difficulty in estimating muscle mass, we would have expected a better result from the MacDonald formula, obtained by adjusting creatinine for body composition data measured by bioelectrical impedance analysis. Value dispersion was quite similar to that of other equations or actually even worse (see error dispersion in box plots, ROC curves and Bland-Altman analysis; figures 1, 3 and 4 respectively). We therefore had to conclude that the determination of muscle mass by bioelectrical impedance analysis did not result in any significant added contribution in estimating GFR in the population under study.

However, taking into consideration the sound theoretical context in favour of the definition and use of such an equation, we wondered why the MacDonald formula proved to be imprecise. The small size of the population used to determine it, the lack of external validation [30], the extreme characteristics of the group which we tested, the possible loss of precision in the analysis of body composition in polymorbid elderly patients [42] and the use of a different software to determine body composition, could all have contributed to increased error dispersion.

The use of bioelectrical impedance analysis to reduce error in creatinine-related GFR estimation, still retains a theoretical attractiveness, and will have to be reassessed in studies based on a wider population representative of the in-hospital one, for which the interest in using a predictive equation is greater.

The second surprise was to observe that the MDRD formula did not offer significant advantages compared to Cockcroft and seems to be less effective when compared with the Larsson one.

The relative imprecision of the MDRD formula might be related to the selected population (American in MDRD and European in Cockcroft and Larsson) or, once again, to the clinical characteristics of the population such as advanced age and polymorbidities of the group in which we performed the evaluation.

The results of the present study once again suggest that the equations obtained from large clinical studies thus show fragility in the extremes – in this case, advanced age and polymorbidities [38]. This is particularly relevant as the group selected for the study (CKD stages III-IV based on

Table 3: Measured versus estimated GFR. GFR measured with inulin and calculated with the selected algorithms and absolute error in performing the estimation. Data are given using non-parametric and parametric values to allow a quantitative comparison; mean and SD values of the absolute error correlate with accuracy and precision respectively.

	Median (25–75% interquartile range) ml/min	Mean ± SD ml/min	Median error (25–75% interquartile range) ml/min	Mean error ± SD ml/min
GFR Inulin	30.9 (22.0–43.3)	34.9 ± 20.0		
GFR CKC	45.1 (34.6–55.3)	46.7 ± 18.5	14.3 (5.55–23.2)	11.8 ± 19.2
GFR CYS	45.9 (31.9–59.4)	47.2 ± 23.0	12.8 (4.50–25.3)	12.4 ± 20.6
GFR BTP	54.2 (42.2–62.4)	54.4 ± 18.2	17.6 (11.5–31.5)	19.5 ± 17.7
GFR MDRD	47.9 (39.5–60.1)	49.0 ± 15.9	16.3 (6.4–27.5)	14.1 ± 19.8
GFR ALM	66.0 (46.3–77.7)	32.9 ± 27.2	32.2 (13.9–45.4)	32.9 ± 27.2

GFR CYS = GFR estimated by Cystatin C; GFR BTP = GFR estimated by Beta Trace Protein; GFR ALM = GFR estimated by Appendicular Lean Mass and creatinine.
GFR CKC = GFR estimated by Cockcroft's algorithm. GFR MDRD = GFR estimated by MDRD (Modification of Diet in Renal Disease) algorithm.

Table 4: Percentage of KDOQI CKD class change [25] obtained correcting the results of the estimations with the gold standard (GFR inulin).

KDOQI Class change	GFR BTP	GFR MDRD	GFRALM	GRFR CYS	GFR CKC
Total class change %	65.3	56.5	75.5	49.3	52.3
+1 class	50.7	46.4	37.7	39.1	37.7
–1 class	1.5	7.2	0	1.5	5.8
+2 classes	11.6	2.9	31.9	7.2	5.8
–2 classes	1.5	0	1.5	1.5	1.5
± >2 classes	0	0	4.4	0	1.5

GFR CYS = GFR estimated by Cystatin C; GFR BTP = GFR estimated by Beta Trace Protein; GFR ALM = GFR estimated by Appendicular Lean Mass and creatinine.
GFR CKC= GFR estimated by Cockcroft's algorithm. GFR MDRD = GFR estimated by MDRD (Modification of Diet in Renal Disease) algorithm.

eGFR MDRD) accounts for 53% of the patients admitted to the internal medicine wards of our hospitals.

Beta-trace protein does not seem to offer specific advantages against creatinine and cystatin C; while the White equation is the only one that does not generate outliers. Unfortunately this latter shows a greater error dispersion in GFR estimation than Cockcroft, Larsson and MDRD.

What are we supposed to do in the face of such a large margin of error? Assuming that the results were not generated by a bias related to the small group of patients analysed or to the single shot method used to measure inulin clearance (see intra-patient dispersion of the GFR determination in the results section); all the equations tested seem to be prone to considerably overestimate GFR. While we can imagine using the ones offering the best performance, we are not safe from either, the risk of intoxicating patients with medications eliminated mainly by the renal route characterised by a narrow therapeutic margin (e.g., some chemotherapics and antibiotics), and in a smaller subgroup, the risk of being, on the contrary, below the therapeutic range. Considering the relevance of the topic and the amount of in-hospital patients matching the selection criteria of the study, further investigation aimed to confirm and more extensively characterising patients with large GFR estimation errors, should be performed.

Therefore, it is of the utmost importance to closely monitor the onset of any toxicity signs; whenever serum concentrations of a medication used cannot be measured and to be ready to adjust its dose or, when necessary, to replace the drug with an alternative one. One important issue in elderly patients is the correction of GFR to a standard body surface area (1.73 m^2) as for example in the MDRD formula. Patients in the extremes of weight do often not have a normal body surface area and in that case drug overdosing may occur as well. In this respect the Cockcroft formula, considering also the weight, could be the safest.

In conclusion, the Cockcroft, Larsson, MDRD, White and MacDonald equations are significantly overestimating kidney function in our CKD stage III–IV inpatient population (average overestimation ranging from 11.4 to 32.9 ml/min; the extremes being Cockcroft and Macdonald respectively). These results are important because the selected population represents at least half of all patients admitted in an internal medicine ward.

The best performance was obtained with the Larsson equation, based on cystatin C. The measurement by bioelectrical impedance analysis of muscle mass, introduced with creatinine in the MacDonald formula, does not allow more accurate results to be obtained, at least in our population of patients.

Clinicians must therefore use estimated GFR with prudence, being ready to discontinue medications with narrow therapeutic margins eliminated by the renal route in all cases of suspected toxicity. New studies designed to improve predictive equations to be used in elderly in-hospital populations should be conducted.

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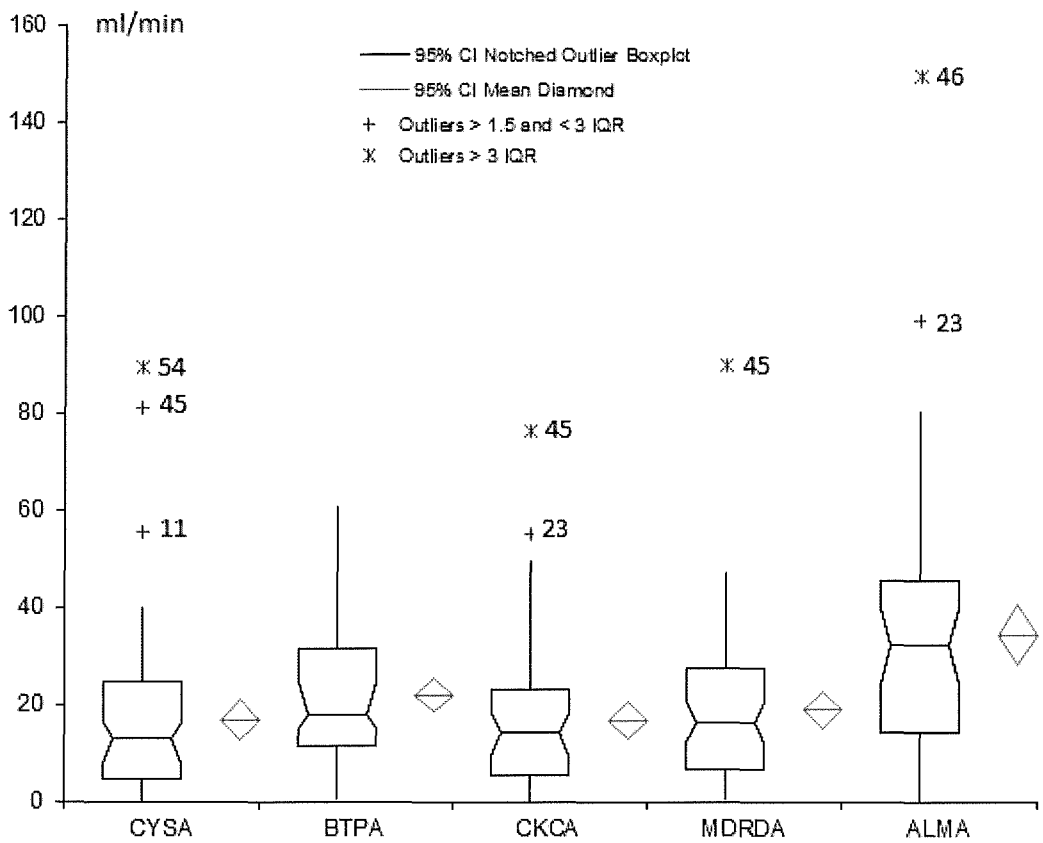
Figures (large format)

Figure 1

Box Plot showing the absolute error in estimating GFR (inulin clearence as the gold standard). CYSA, BTPA, CKCA, MDRDA, ALMA = absolute error in estimating the GFR using algorithms based respectively on Cystatin C; Beta-trace protein, creatinine and anthropometric values (Cockcroft); creatinine and anthropometric values (MDRD), creatinine, anthropometric values and appendicular lean mass (approximating muscle mass) measured by bioimpedance.
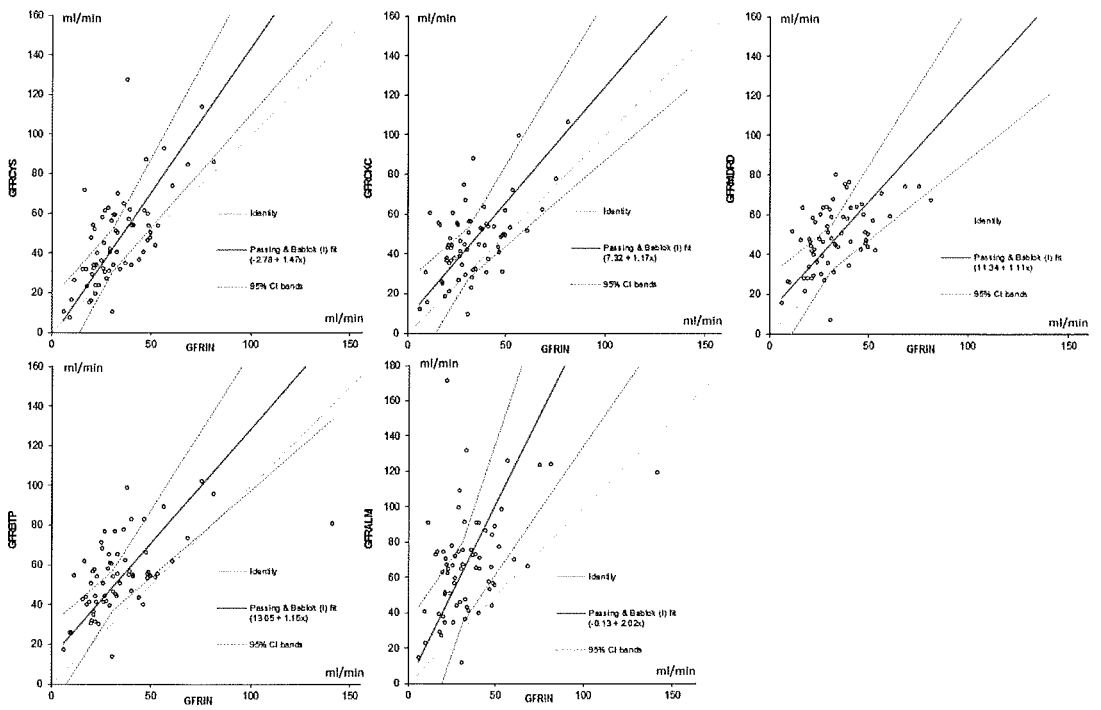
Figure 2

Scatterplots comparing the estimations obtained with the tested algorithms to the GFR measured by inulin; the diagonal line indicates the equality. A Passing and Bablok analysis shows the trend of the distribution and its 95% confidence intervals.
GFR CYS = GFR estimated by Cystatin C; GFR BTP = GFR estimated by Beta Trace Protein; GFR ALM = GFR estimated by Appendicular Lean Mass and creatinine. GFR CKC= GFR estimated by Cockcroft's algorithm. GFR MDRD = GFR estimated by MDRD (Modification of Diet in Renal Disease) algorithm.
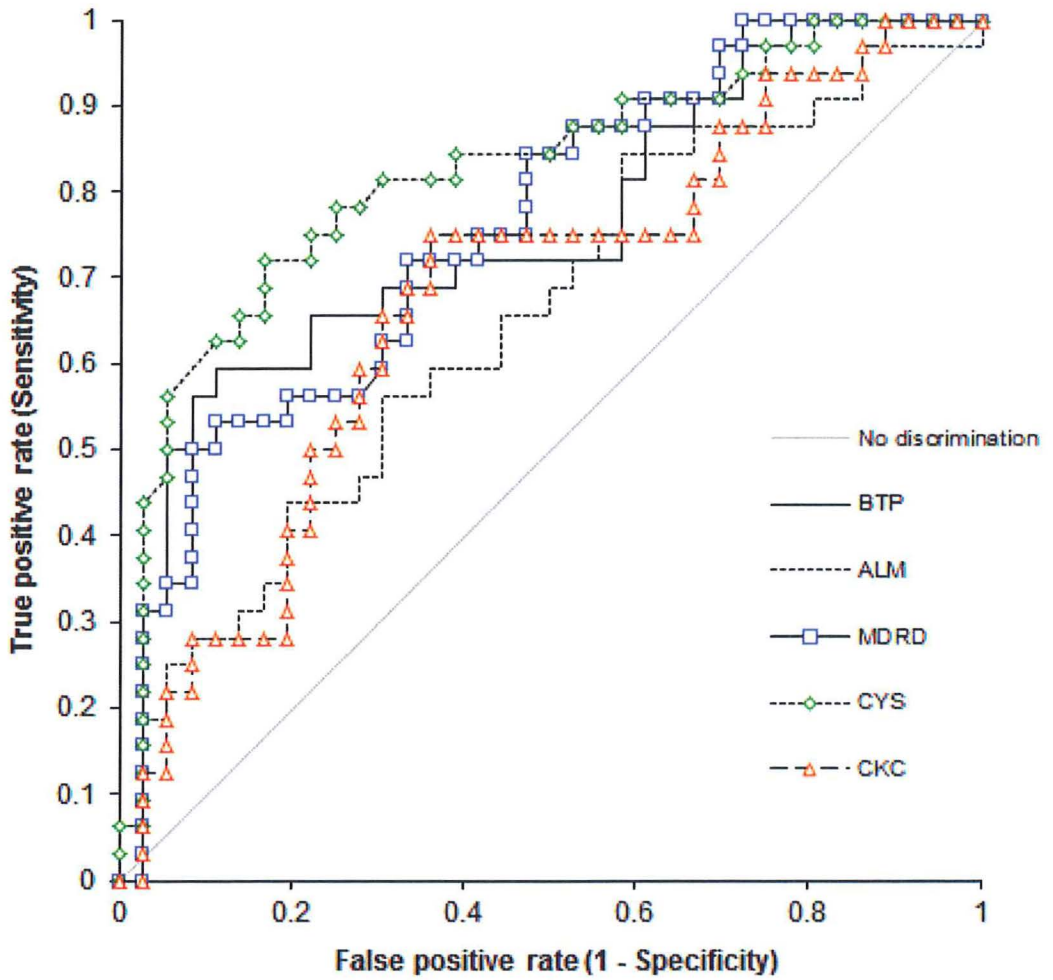
Figure 3

ROC Curves plotting the sensitivity against 1 minus the specificity of the selected algorithms in predicting an inulin clearance <30 ml/min. CYS = GFR estimated by Cystatin C; BTP = GFR estimated by Beta Trace Protein; ALM = GFR estimated by Appendicular Lean Mass and creatinine. CKC= GFR estimated by Cockcroft's algorithm. MDRD = GFR estimated by MDRD (Modification of Diet in Renal Disease) algorithm. The ideal test would have an AUC of 1, whereas a random guess would have an AUC of 0.5.
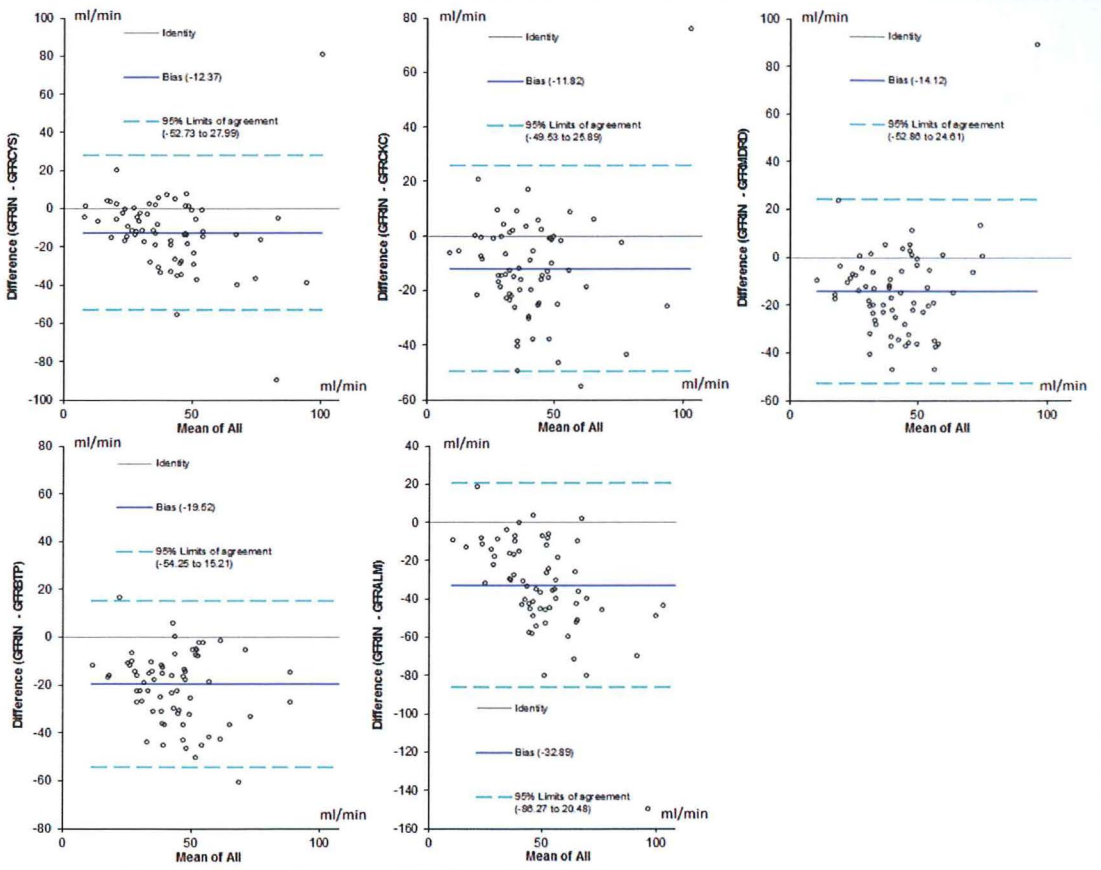
Figure 4

Bland and Altman analysis. In this analysis the differences between the gold standard and the selected prediction algorithm, are plotted against the mean of measured and calculated GFR for each individual patient.

GFR CYS = GFR estimated by Cystatin C; GFR BTP = GFR estimated by Beta Trace Protein; GFR ALM = GFR estimated by Appendicular Lean Mass and creatinine. GFR CKC= GFR estimated by Cockcroft's algorithm. GFR MDRD = GFR estimated by MDRD (Modification of Diet in Renal Disease) algorithm.