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CONTRAST MEDIA

Assessment of renal function before contrast media injection: right decisions based on inaccurate estimates

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Abstract

Objectives Information on renal function required before specified radiological examinations with contrast agents is usually obtained through prediction equations using serum creatinine and anthropometric data. The aim of our study was to demonstrate discrepancy between poor prediction and good diagnostic accuracy of glomerular filtration rate (GFR) estimated by prediction equations.

Methods In 50 patients, reference GFR was measured as plasma clearance of 51-chromium labeled ethylene-diamine-tetraacetic-acid (^{51}Cr-EDTA) and compared with GFR assayed by creatinine clearance (CC) and estimated by Cockcroft-Gault prediction equation (CG). For comparisons, CC and CG were considered as continuous, categorical, and binary variables. Accuracy of the reference GFR prediction was expressed in terms of prediction errors and diagnostic accuracy indices.

Results As *continuous* variable, CG estimated individual values of GFR with large prediction error exceeding that of CC. As *categorical* variable, it classified the patient stage of chronic kidney disease (CKD) with medium diagnostic accuracy of 74% (CKD 3) and 62% (CKD 4). As *binary* variable, CG classified individual patient's GFR below 30 and 60 ml/min/1.73 m^2 with good diagnostic accuracy of 80 and 94%, respectively. Performance of other prediction equations did not significantly differ from CG.

Conclusions Despite large variance and poor prediction accuracy of individual GFR estimates, most of them correctly classified individual patient's GFR below specified level. Results of prediction equations thus should be used and reported exclusively as binary variables, while numerical values of GFR, if required, should be measured by more accurate radionuclide or laboratory methods.

Key Points

- *Radiological guidelines on contrast media require estimation of glomerular filtration rate to assess kidney function before specified contrast examinations.*
- *Estimated glomerular filtration rate is obtained through prediction equations using serum creatinine and anthropometric data as predictors.*
- *While numerical estimates of glomerular filtration rate are inaccurate (their prediction accuracy is poor), diagnostic accuracy of binary estimates (ability to classify patient's glomerular filtration rate below or above a specified level) is very good.*

Keywords Kidney function tests · Glomerular filtration rate · Creatinine · Contrast media

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Abbreviations

^{51}Cr-EDTA	Ethylene-diamine-tetraacetic acid labeled by chromium-51
AUROC	Area under the receiver operating characteristics (ROC) curve
CC	Creatinine clearance
CG	Cockcroft-Gault prediction equation
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration prediction equation
DGA	Diagnostic accuracy
EDTA	^{51}Cr-EDTA clearance measured by two blood samples (reference GFR)
GFR	Glomerular filtration rate
LM	Lund-Malmö prediction equation
LM-LBM	Lund-Malmö prediction equation with lean body mass
MAE	Mean absolute error of prediction
MDRD	Modification of Diet in Renal Disease prediction equation
MQ	Mayo Quadratic equation
MRE	Mean relative error of prediction
NPV	Negative predictive value
PPV	Positive predictive value
r	Correlation coefficient
Se	Sensitivity
Sp	Specificity

Introduction

European Society of Urogenital Radiology Guidelines on Contrast Media require estimation of glomerular filtration rate (GFR) to assess the patient's kidney function before specified contrast examinations [1]. Estimated GFR is obtained through prediction equations using serum creatinine and anthropometric data as predictors. Prediction equations were introduced in the 1970's by Jelliffe and Jelliffe [2], Cockcroft and Gault [3], and Schwartz et al [4]. Since then, a variety of prediction equations were developed for both adults and children [5]. Accuracy and comparative studies of prediction equations have been published and the recommendations for GFR estimation summarized in clinical practice guidelines on chronic kidney disease [6–8].

An advantage of prediction equations is their simplicity. A disadvantage is limited accuracy (i.e., ability to predict individual patient's GFR), especially in the patients with unstable renal function and pathological conditions of the kidneys [5]. Froissart et al [9] compared the results of Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault (CG) prediction equations with ^{51}Cr-EDTA GFR in 2095 European subjects suffering from chronic kidney disease (CKD), and found only 70% of them classified in the correct stage. Confidence interval (95%) for GFR = 60 ml/min estimated by MDRD equation extended from 35 to 90 ml/min. Poggio et al [10] compared MDRD and CG equations with ^{125}I-iothalamate GFR in 1285 patients. In the patients with measured GFR below 60 ml/min, they found small bias but accuracy within ± 30% of the measured values in only 71% (MDRD) and 60% (CG) of patients, while 11% (MDRD) and 23% (CG) values exceeded the limits of ± 50%. Craig et al [11] found good correlation between GFR estimated by MDRD and GFR measured by radionuclides in 468 patients but significant overestimation of the measured GFR and 95% of individual differences in a wide range from -19.2 to + 40.7 ml/min/1.73 m^2. Due to poor prediction accuracy documented by such studies, it has been recommended to report estimated GFR over 60 ml/min as "greater than or equal 60 ml/min," and the values below 60 ml/min just as "decreased" [6, 12].

In contrast to poor prediction accuracy, several authors found reasonably good diagnostic accuracy of prediction equations (i.e., ability to classify individual patient's GFR below or above a specified value). Hoek et al [13] found area under ROC curve for GFR cut level 60 ml/min/1.73 m^2 as high as 0.92 for creatinine and 0.96 for CG and cystatin-C equations. Nyman et al [14] were able to detect the patients with GFR below 60 ml/min/1.73 m^2 using Lund-Malmö equation with sensitivity 92%, specificity 89%, and the area under ROC curve 0.97. The aim of our study was to analyze apparent discrepancy between poor prediction accuracy and good diagnostic accuracy of GFR estimates and provide additional contribution to their understanding and reliable use in clinical practice.

Methods

In a retrospective study, anonymized data of 50 patients indicated to radionuclide examination of the kidneys were analyzed. Collection and subsequent analysis of anonymous data was approved by local Ethics Committee and informed consent waived for retrospective nature of the study. The data used for the study are available from public database [15] and as electronic supplementary material of this article. The group of patients with complete laboratory and radionuclide examinations included 22 men and 28 women in the age of 21–86 years with a wide range of renal pathology and function (creatinine clearance 3–153 ml/min/1.73 m^2).

Present gold standard to assess renal function is to measure plasma clearance of radiopharmaceuticals or iodinated contrast agents (iothalamate, iohexol) excreted predominantly by glomerular filtration [16–18]. Reference method chosen in this study was the clearance of ^{51}Cr-EDTA with respect to its high accuracy, small amount of blood required for activity measurement, negligible effective radiation dose to the patients, and long chromium-51 half-life that makes possible to

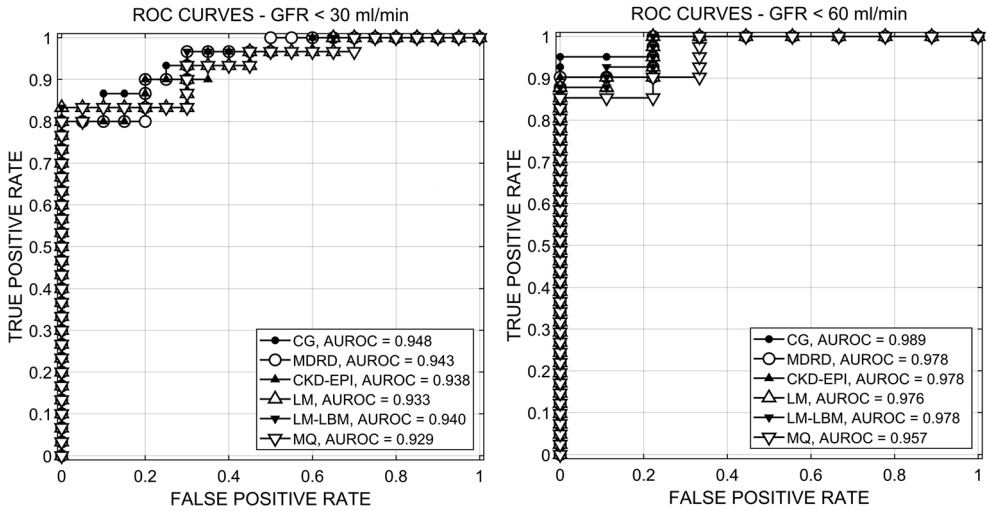

Fig. 1 ROC curves demonstrating performance of six prediction equations examined in the study to detect GFR below 30 ml/min/1.73 m^2 (left panel) and below 60 ml/min/1.73 m^2 (right panel)

prolong blood sampling if required in the patients with low renal function. The method consists in activity measurement of one, two, or several blood samples withdrawn during several hours after single intravenous injection of ^{51}Cr-EDTA. After the tracer concentration equilibrates between plasma and extravascular fluids, decreasing plasma concentration of ^{51}Cr-EDTA reflects total kidney GFR. Two blood samples obtained 2- and 4-h post injection were used as a compromise between accuracy and complexity of the method. Reference values of ^{51}Cr-EDTA GFR (EDTA) were calculated using the method by Jødal and Brøchner-Mortensen [19, 20]. Besides EDTA, GFR was measured by standard laboratory test of creatinine clearance with 24-h urine collection (CC). Serum creatinine was assayed by Jaffe method, IDMS-calibrated (isotope dilution mass spectrometry), Roche, and its results substituted into prediction equations together with anthropometric data on the patients. Median time interval between radionuclide and laboratory examinations was 1 day.

GFR was estimated by six prediction equations: (1) Cockcroft-Gault (CG) equation normalized to standard body-surface area [3], (2) standardized IDMS traceable four-variable Modification of Diet in Renal Disease (MDRD) equation [21, 22], (3) Chronic Kidney Disease—Epidemiology Collaboration (CKD-EPI) equation [23], (4) Lund-Malmö equation (LM) and (5) Lund-Malmö equation with lean body mass (LM-LBM) [24], and (6) Mayo Quadratic equation (MQ) [25]. All GFR values were normalized to standard body surface area of 1.73 m^2. No potential outliers were excluded.

The results of prediction equations and CC were compared with reference values of EDTA as continuous, categorical, and binary variables. Performance criteria for *continuous variables* (numerical values of GFR in individual patients) were correlations with the reference values and the mean absolute and relative errors of prediction (MAE, MRE) estimated using cross validation [26, 27]. Cross validation effectively simulates conditions of a prospective study and provides realistic estimates of prediction errors generated by future examinations not included in the retrospective data. *Categorical variables* (the values of GFR distributed into five CKD categories—below 15, 15–29, 30–59, 60–89, 90 and above ml/min/1.73 m^2) were tested for diagnostic accuracy of CKD staging. *Binary variables* (the values of GFR divided to only two categories—below

Table 1 Accuracy of creatinine clearance (CC) and Cockcroft-Gault prediction equation (CG) to predict numerical values of GFR obtained by reference method (EDTA)

test	GFR all data ($n = 50$)			GFR < 30 ml/min ($n = 29$)			GFR ≥ 30 ml/min ($n = 21$)		
	r	MAE (ml/min)	MRE (%)	r	MAE (ml/min)	MRE (%)	r	MAE (ml/min)	MRE (%)
CC	0.93 (0.88–0.96)	7.7 (5.5–9.9)	28 (20–36)	0.68 (0.42–0.84)	4.1 (2.9–5.3)	27 (15–38)	0.87 (0.70–0.95)	10.9 (6.4–15.4)	20 (10–29)
CG	0.87 (0.78–0.92)	10.4 (6.7–14.1)	33 (24–43)	0.70 (0.45–0.85)	4.0 (2.9–5.1)	27 (16–39)	0.73 (0.43–0.88)	17.9 (9.6–26.2)	31 (17–44)

Each entry (correlation coefficient r, mean absolute error of prediction MAE, mean relative error of prediction MRE) represents the mean value and 95% confidence intervals of the mean in the three groups: all patients ($n = 50$), the patients with GFR below 30 ml/min/1.73 m^2 ($n = 29$), and GFR equal or above 30 ml/min/1.73 m^2 ($n = 21$)

Table 2 Diagnostic accuracy of creatinine clearance (CC) and Cockcroft-Gault prediction equation (CG) to classify the patients to chronic kidney disease stage CKD 4 (GFR 15–29 ml/min/1.73 m^2) and CKD 3 (GFR 30–59 ml/min/1.73 m^2) as compared with the classification by the reference method of EDTA

test	15 ml/min ≤ GFR < 30 ml/min (n = 19/50)						30 ml/min ≤ GFR < 60 ml/min (n = 12/50)					
	Se	Sp	PPV	NPV	DGA	AU ROC	Se	Sp	PPV	NPV	DGA	AU ROC
CC	26	90	63	67	66	74	75	79	53	91	78	78
CG	37	77	50	67	62	75	75	74	47	90	74	76

Each test was performed with all patients (n = 50) to detect true positive cases that belong to CKD 4 (n = 19) and CKD 3 (n = 12). Each entry represents respective parameter of diagnostic accuracy in %

and above a specified level) were tested for diagnostic accuracy of correct classification of GFR into one of the two categories. ROC curves and their parameters for categorical and binary variables were calculated using Matlab [27]. Due to the number of our patients in individual CKD stages and due to their clinical importance in the context of radiology, CKD 3 (GFR 30–59 ml/min/1.73 m^2) and CKD 4 (GFR 15–29 ml/min/1.73 m^2), and the limits of 30 and 60 ml/min/1.73 m^2 were chosen for evaluation.

Results

The results of all prediction equations were closely correlated (r = 0.83–0.99) and the differences between their mean prediction errors were not statistically significant (p > 0.05). To simplify subsequent comparisons, CG has been chosen to represent the examined group of prediction equations because of its high area under ROC curve in binary decisions (Fig. 1). Other prediction equations demonstrated their relative merits and weaknesses, mostly marginal: CKD-EPI produced numerical results with lower prediction errors while LM and LM-LBM equations demonstrated good diagnostic accuracy of CKD classification and high negative prediction value of binary decisions (84 and 88% of the patients with estimated GFR above 30 and 60 ml/min/1.73 m^2 had indeed their true GFR above these limits). The tables with complete results of all prediction equations are presented as supplementary material.

Performance of CC and CG as *continuous variables* is demonstrated in Table 1 in terms of correlations and prediction errors in all subjects (n = 50), and in the two subgroups of patients with EDTA lower than 30 ml/min/1.73 m^2 (n = 29) and greater than or equal 30 ml/min/1.73 m^2 (n = 21). With GFR below 30 ml/min/1.73 m^2, both methods performed equally well. With GFR equal or above 30 ml/min/1.73 m^2, CC significantly outperformed CG with lower prediction errors: prediction interval around the reference value of GFR including 95% of individual GFR values extended from -10 to +32 ml/min/1.73 m^2 with CC and from -21 to +57 ml/min/1.73 m^2 with CG. Despite low number of patients in this study, extremely wide limits are similar to those reported in the previous studies.

Performance of CC and CG as *categorical variables* to classify a patient into a specified category (CKD stages 3 and 4) is summarized in Table 2. CG correctly classified 74% (CKD 3) and 62% (CKD 4) of the patients while CC was only marginally better (78% and 66%, respectively).

Performance of CC and CG as *binary* variables to classify a patient's GFR below or above a specified value of 30 and 60 ml/min is demonstrated in Table 3. Both variables performed well with diagnostic accuracy of 82% (CC) and 80% (CG) for the limit of 30 ml/min/1.73 m^2, and 96% (CC) and 94% (CG) for the limit of 60 ml/min/

Table 3 Diagnostic accuracy of creatinine clearance (CC) and Cockcroft-Gault prediction equation (CG) to classify the patient's GFR below 30 and 60 ml/min/1.73 m^2 as compared with the reference method of EDTA

test	GFR < 30 ml/min (n = 29/50)						GFR < 60 ml/min (n = 41/50)					
	Se	Sp	PPV	NPV	DGA	AU ROC	Se	Sp	PPV	NPV	DGA	AU ROC
CC	72	95	95	71	82	97	95	100	100	82	96	99
CG	66	100	100	68	80	97	93	100	100	75	94	99

Each test was performed in all patients (n = 50) to detect true positive findings with GFR below 30 ml/min/1.73 m^2 (n = 29) and 60 ml/min/1.73 m^2 (n = 41). Each entry represents respective parameter of diagnostic accuracy in %

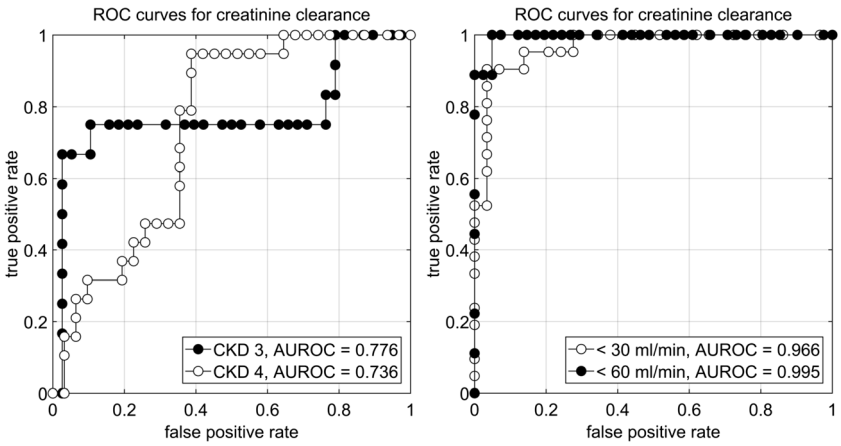

Fig. 2 ROC curves demonstrating performance of creatinine clearance to classify the patient into the CKD stages 3 and 4 as categorical variable (left panel) and the patient's GFR below 30 and 60 ml/min/1.73 m^2 as binary variable (right panel)

1.73 m^2. The patients with GFR reduced below 30 ml/min/1.73 m^2 and 60 ml/min/1.73 m^2 were indicated with high positive predictive value of 95–100% while the negative predictive value was lower (68–71% and 75–82%, respectively).

ROC curves for CC and CG tests are presented in the Figs. 2 and 3. They demonstrate poor diagnostic accuracy of the patient classification into CKD 3 and 4 and good diagnostic accuracy of the binary decision that individual patient's GFR falls below 30 and 60 ml/min/1.73 m^2.

Discussion

With a single group of patients, this study demonstrates highly variable performance of prediction equations that depends on interpreting their results as continuous, categorical, or binary variables. It provides explanation of previously observed discrepancy between poor prediction accuracy of numerical GFR estimates in individual patients (large prediction errors and extremely wide prediction intervals of individual values), and good diagnostic accuracy when the patient's GFR was simply placed below or above a specified level. Our results confirm previous observations that GFR prediction equations (here represented by CG) perform best when responding a question "*Is this patient's GFR lower than 60 ml/min/1.73 m2?*" rather than more common but inappropriate question "*What is the GFR value in this patient?*"

Simple explanation of apparent inconsistency between good binary decision and poor numerical accuracy is illustrated in the Fig. 4. Data points are simulated to approximate pooled results of several previous studies with large number of patients [9–11]. The left panel of Fig. 4 demonstrates that while estimated GFR of 60 ml/min/1.73 m^2 may indicate true GFR anywhere between 30 and 90 ml/min/1.73 m^2 (an information virtually useless), for estimated GFR values below or above the same value of 60 ml/min/1.73 m^2 (right panel), vast majority of true values are indeed below or above 60 ml/min/1.73 m^2 (representing true positive and true negative findings that clearly dominate over relatively scarce false negative and false positive findings). As binary variables, prediction equations offer good diagnostic accuracy for minimum expenses.

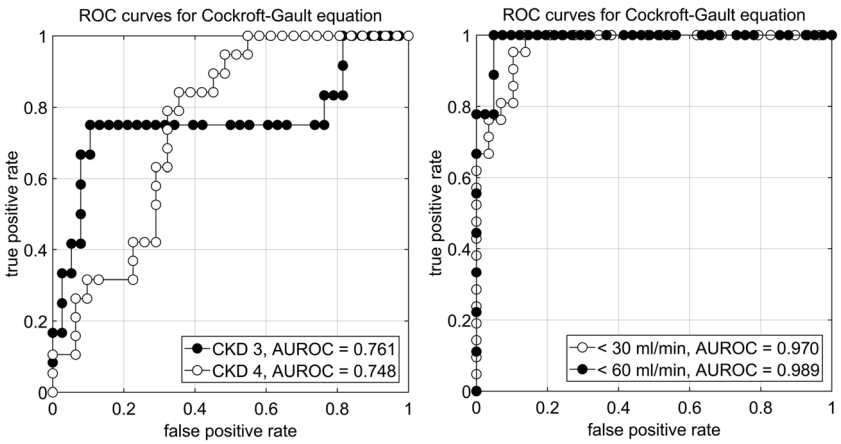

Fig. 3 ROC curves demonstrating performance of Cockcroft-Gault prediction equation to classify the patient into the CKD stages 3 and 4 as categorical variable (left panel), and the patient's GFR below 30 and 60 ml/min/1.73 m^2 as binary variable (right panel)

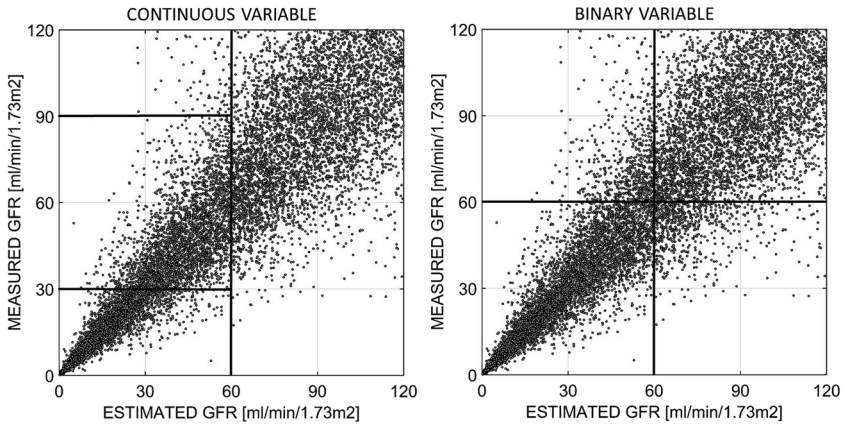

Fig. 4 Interpretation of estimated GFR as continuous (left panel) and binary variable (right panel). Individual points represent individual patient's measured and estimated GFR simulated to approximate the results of large studies [9–11]. Numerical point estimates of individual patient's GFR values (left panel) are variable and inaccurate: confidence interval 95% for estimated GFR value of 60 ml/min/1.73 m^2 (vertical line) is 30–90 ml/min (as shown by horizontal lines). However (right panel), when considering GFR estimate as binary variable (with only two values—here lower or greater than 60 ml/min/1.73 m^2), then most GFR estimates below or above 60 ml/min are indeed below (lower left quadrant = true positive findings) or above (upper right quadrant = true negative findings) the specified value indicating and explaining good diagnostic accuracy of a binary decision

Limitation of our study is a low number of patients and high prevalence of low kidney function (82% of the patients had GFR below 60 ml/min/1.73 m^2). However, our findings correspond well with the results of large studies published before (not interpreted in terms of continuous, categorical, and binary variables). For example, prediction interval of individual patient's GFR estimates found in our study (-21 to +57 ml/min/1.73 m^2) is similar to those reported by Froissart et al [9] in 2095 patients (approx. -28 to +30 ml/min/1.73 m^2) and by Craig et al [11] in 468 patients (-19.2 to +40.7 ml/min/1.73m^2 with the difference range of -16.8 to +88.3 ml/min/1.73m^2 just in the stage CKD 3). It may indicate that low prediction accuracy is inherent to GFR estimation based on creatinine rather than due to the limited number of patients in our study. High prevalence of low kidney function in our group of patients may be responsible for higher positive and lower negative predictive values in binary decisions. If that is so, it should not affect application of prediction equations in radiology where the prevalence of low kidney function in general patient population is expected to be lower (though not necessarily in all age groups and disease types). Avoiding false negative results of examination (indicating high GFR when it is low) should be imperative in radiological applications. The future research should therefore focus on Lund-Malmö equations (especially one with lean body mass) that provided the highest negative predictive values (cf supplementary material).

Performance of prediction equations in binary decisions may be further improved by detecting optimal operating points and decision thresholds which may not necessarily correspond to the limits of CKD stages (15, 30, 60, and 90 ml/min/1.73 m^2). For example, in our group of patients, negative predictive value of CG to classify patient's GFR below 60 ml/min/1.73 m^2 was 75% (Table 3). After optimal operating point was detected and diagnostic accuracy maximized, NPV increased to 100% (Table 4). Similar procedure increased NPV of other prediction equations to detect GFR < 60 ml/min/1.73 m^2 from 64–88% to 100% (cf supplementary material). Another possibility to improve performance of prediction equations in binary decisions would be to apply the methods of predictive analysis [27]. However, both optimization and predictive analysis would require substantially higher number of patients and examinations than we were able to collect for simple analysis of performance with three different types of variables.

Table 4 Diagnostic accuracy of creatinine clearance and Cockcroft-Gault prediction equation (CG) to classify the patient's GFR below 30 and 60 ml/min/1.73 m^2 as compared with the reference method of EDTA

test	GFR < 30 ml/min (n = 29/50)						GFR < 60 ml/min (n = 41/50)					
	Se	Sp	PPV	NPV	DGA	AU ROC	Se	Sp	PPV	NPV	DGA	AU ROC
CC	97	90	93	95	94	97	100	89	98	100	98	99
CG	83	100	100	81	90	97	100	78	95	100	96	99

The table presents maximum diagnostic accuracy values using optimized thresholds of positivity. Each entry represents respective parameter of diagnostic accuracy in %

With their limitations in mind, prediction equations can be used to test kidney function before contrast examinations in radiology with similar safety as creatinine clearance. On the other hand, whenever the correct numerical value of GFR is required—as, for example, in calculating the doses of nephrotoxic drugs in anti-tumor therapy, in assessment of renal function in kidney donors—but also in the high-risk patients and procedures in radiology, a proper radionuclide or laboratory examination of GFR should be used instead.

Conclusion

The results of prediction equations should be used and reported as binary variables indicating with good diagnostic accuracy the true GFR below or above a specified level. In this study, we have demonstrated 80% and 94% diagnostic accuracy of Cockcroft-Gault equation to indicate true GFR below or above 30 and 60 ml/min/1.73 m^2, respectively, while the same method suffered from the large prediction error over the most of GFR spectrum. Other commonly used prediction equations examined in this study (MDRD, CKD-EPI, LM, LM-LBM, and MQ) performed in a similar way. If a numerical value of GFR and correct classification of the patient to a specific CKD stage is required, GFR should be measured by radionuclide or laboratory methods.

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Compliance with ethical standards

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Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was not required for this study because of its retrospective nature.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Part of the results has been published as short abstract of poster contribution to the congress of European Association of Nuclear Medicine.

Methodology
- retrospective (using cross-validation)
- diagnostic study
- performed at one institution

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