

Estimation of kidney function in cancer patients

Belén Redal-Baigorri¹, Knud Heine Stokholm², Knud Rasmussen¹ & Nina Jeppesen³

ABSTRACT

INTRODUCTION: The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula has not been validated in patients with cancer. The present investigation was undertaken in order to study how well estimated glomerular filtration rate (eGFR) using the new CKD-EPI equation correlates with measured GFR (mGFR) by ⁵¹Cr-EDTA clearance in a group of patients with cancer not known as having chronic kidney disease.

MATERIAL AND METHODS: We investigated 185 patients with cancer who were referred for isotope measurement of GFR with ⁵¹Cr-EDTA before initiating chemotherapy treatment. The agreement between CKD-EPI and ⁵¹Cr-EDTA was assessed using a Bland-Altman plot. Test performance was analysed in a contingency table and bias, precision and the percentage of estimates within 30% of the mGFR (P30) were assessed.

RESULTS: Bland-Altman plot analysis showed a limit of agreement in the range from -25.59 to 27.92 ml/min./1.73 m². This formula was therefore not interchangeable with ⁵¹Cr-EDTA, as the above differences are of clinical importance. Bias was low: 1.16 ml/min./1.73 m²; P30 was high: 89.73%; and precision was 13.37 ml/min./1.73 m². As a screening test, the CKD-EPI had a high specificity of 98% (95% confidence interval (CI): 96 to 100%) and a high negative predictive value 97% (95% CI: 95 to 100%). The accuracy of the validation test was 96% (95% CI: 93 to 99%).

CONCLUSION: The CKD-EPI may be used as a screening tool for CKD in the general population, but cannot replace isotope tests when a high GFR measurement accuracy is needed.

Chronic kidney disease (CKD) is a major public health issue. In oncology, it is mandatory to ascertain whether a patient has CKD before considering treatment with platinum-based compounds due to the risk of developing nephrotoxicity [1].

In the initial work-up, the patient's glomerular filtration rate (GFR) should be measured, but GFR measurements are cumbersome and therefore not easily performed in clinical practice. Inulin clearance is the gold standard, but it is expensive and it is difficult and time-consuming to measure inulin clearance regardless of which technique is used [2].

Novel methods using radioactive tracers such as ⁵¹Cr-EDTA

[3, 4] and radio contrast agents such as iohexol [5] are also time-consuming since patients have to wait three to five hours or even 24 hours after injection of the tracer before blood samples can be drawn.

Because of these obstacles, prediction formulas based on serum creatinine have emerged.

One of the earliest such formulas is the Cockcroft and Gault formula [6] which estimates creatinine clearance.

In 1999, Levey et al [7] proposed the Modification of Diet in Renal Disease (MDRD) formula for estimation of the GFR (eGFR). The formula is based on 1,628 patients with a mean GFR of 39.8 ml/min./1.73 m². Its performance has been validated for GFRs below 60 ml/min./1.73 m², but the validity of the formula has been questioned in patients with a normal or near normal GFR [8].

In 2009 a new equation was presented: Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), which is based on a sample size of 8,254 patients with a median measured GFR (mGFR) of 68 ± 40 ml/min./1.73 m² [9].

Whether GFR estimation with creatinine-based methods such as MDRD or GFR may replace the GFR measurement has been widely investigated in a range of patient groups, but studies addressing this issue in oncology are lacking. The present study was undertaken to explore, using the new CKD-EPI equation, how well eGFR correlates with mGFR by ⁵¹Cr-EDTA in a group of patients not previously diagnosed with severe CKD and newly diagnosed with cancer. Furthermore, the validity of the CKD-EPI formula as a screening tool was evaluated.

Our Department of Oncology refers about 150-200 patients per year to GFR measurement by ⁵¹Cr-EDTA prior to platinum-based drug treatment. mGFR expressed in absolute values is then used to calculate the carboplatin dose and to determine if there is indication for cisplatin treatment. If mGFR is below 50 ml/min, cisplatin is not administered.

MATERIAL AND METHODS

Study design

The study is a retrospective analysis based on data from cancer patients collected before they started chemotherapy with cisplatin or carboplatin. The study was approved by the Danish Data Protection Agency (j. no.

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1) Department of Medicine, Division of Nephrology, Roskilde Hospital, 2) Department of Clinical Physiology and Nuclear Medicine, Køge Hospital, and 3) Department of Oncology and Haematology, Roskilde Hospital

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2007-41-1006). The study was conducted in agreement with the principles of the Declaration of Helsinki.

Participants

A total of 362 patients were referred for determination of GFR by ^{51}Cr -EDTA in the period from 1 January 2006 to 31 December 2007. All patients were examined at the same laboratory.

The inclusion criteria were: Age ≥ 18 years; a minimum of two serum creatinine values with less than 15% variation in range within a period of three months and a serum creatinine value measured a maximum of three weeks before the ^{51}Cr -EDTA measurement. We only used the first value of ^{51}Cr -EDTA in those cases where this test was performed more than once.

Exclusion criteria: Only one creatinine value determination; acute renal insufficiency; diabetic ketoacidosis; increased values of protein (plasma (P) protein > 90 g/l), glucose (P glucose > 17 mmol/l), bilirubin (P bilirubin > 65 micromol/l) or uric acid (P uric acid > 0.45 mmol/l); renal replacement therapy; pregnancy; amputation; treatment with cephalosporins, cimetidine, methyldopa or trimethoprim.

The study population had not been diagnosed with end-stage renal disease (ESRD), as renal replacement therapy was an exclusion criterion. None of the patients were undergoing treatment with erythropoietin (EPO) or active D vitamin at the time of inclusion.

A total of 189 consecutive patients fulfilled the inclusion criteria. Four were excluded due to a high serum level of uric acid, leaving 185 included patients for analysis.

Estimated glomerular filtration rate

Analysis of serum creatinine

Serum creatinine was measured with the Jaffé method (Abbott Architect C systems TMc8000, reagent 7D64). The Jaffé method was calibrated with Isotope Dilution Mass Spectrometry (IDMS) [10].

Calculation of estimated glomerular filtration rate

The MDRD and CKD-EPI formulas have previously been validated in patients with CKD stage 3 or lower-stage CKD, defined as $\text{GFR} \leq 59$ ml/min./1.73 m². Validation was set at this level because higher values are associated with increased imprecision. Even so, these formulas cannot be used alone to define CKD when eGFR is above 60 ml/min./1.73 m² (CKD stages 1-2). In such cases, to establish CKD, other symptoms of kidney disease such as proteinuria or haematuria must be present alongside with eGFR.

CKD-EPI equation: $\text{eGFR} = 141 \times \min(\text{Scr}/k, 1)^a \times \max(\text{Scr}/k, 1)^{-1.209} \times 0.993^{A_{\text{age}}} \times 1.018$ [if female] $\times 1.159$ [if black].

Where Scr is serum creatinine, k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/k or 1 and max indicates the maximum of Scr/k or 1.

Modification of diet in renal disease formula (14) based on serum creatinine (S_c), age, gender and race:

$\text{eGFR (ml/min./1.73 m}^2) = 175 \times (S_c/88.4)^{-1.154} \times \text{age}^{-0.203} \times 0.742$ [if female] $\times 1.21$ [if black].

Where S_c is in micromol/l; 88.4 is the molecular weight of S_c and age is stated in years.

Body surface area (BSA) was calculated from the DuBois & DuBois formula [11] with height in centimetres rather than metres, as $\text{BSA (m}^2) = 0.007184 \times \text{height (cm)}^{0.725} \times \text{weight (kg)}^{0.425}$.

Glomerular filtration rate

GFR was determined from the total (renal and extra-renal) ^{51}Cr -EDTA plasma clearance (Cl_{EDTA}) by a simplified single-injection technique with a single-plasma sample [4]:

$$(\text{Cl}_{\text{EDTA}}) = -\ln(C(t) \times \text{ECV}/Q_0) \times \text{ECV} / (t \times g)$$

Where C(t) are the counts per minute per ml plasma of ^{51}Cr -EDTA at time t; ECV is the extracellular volume; Q_0 is the total amount (counts per minute) of injected ^{51}Cr -EDTA; g is a correcting factor for the difference between the actual t and the theoretical mean sojourn time of ^{51}Cr -EDTA.

$$\text{ECV} = 10,800 \times \text{BSA} - 5,578.6$$

$$g = 0.324 \times e^{-0.0121 \times t} + 1.13 \times e^{-0.000289 \times t}$$

The total ^{51}Cr -EDTA plasma clearance was corrected for gender differences in plasma volume (PV) according to Brøchner-Mortensen [3]:

$$\text{Cl}_{\text{EDTA-PV}} = \text{Cl}_{\text{EDTA}} \times (0.00002512 \times \text{PV} + 0.9246)$$

where PV is determined by multiplying body weight with 41 in females and with 45 in males. The intravenous injection of 3.7 MBq ^{51}Cr -EDTA was given in the morning and a blood sample was drawn after three to four hours.

Statistics

A Bland-Altman plot [12] was used to show the individual differences between eGFR and mGFR. Results are shown as mean \pm standard deviation (SD). p values < 0.05 were considered significant.

The validity of eGFR as a screening test for GFR was calculated from 2×2 contingency tables. Overall agreement in terms of screening was expressed as accuracy, defined as the sum of true positive and true negative findings in percentages of the total number of patients [13].

Confidence intervals (CI) were calculated as Gaussian approximations for single proportions [14].

Bias, precision and accuracy of eGFR with CKD-EPI equation: Bias was defined as the mean difference between the eGFR (CKD-EPI) and mGFR (^{51}Cr -EDTA), whereas precision was expressed as the SD of the mean difference between the eGFR (CKD-EPI) and the mGFR (^{51}Cr -EDTA), or the SD of the bias. A large width equals a low precision. Both precision and bias were expressed as ml/min./1.73 m².

Accuracy was defined as the percentage of patients who had an estimated kidney function within 30% limits of the mGFR (^{51}Cr -EDTA).

RESULTS

Patient characteristics

As shown in **Table 1**, the mean patient age exceeded 60 years, and there was a higher proportion of females than males. The mean mGFR was 85.12 ± 20.31 ml/min./1.73 m².

The types of cancer diagnosed in this population were lung cancer (77%), ovarian cancer (15%) and cancer of the testis (4%).

Validation of Chronic Kidney Disease Epidemiology Collaboration as a laboratory parameter

The Bland-Altman plot is recommended for comparison of two methods with a view to ascertaining whether they agree sufficiently to allow one to replace the other. The present article therefore does not offer correlation coefficients which would be misleading [12].

The mean difference between eGFR and mGFR was 1.16 ml/min./1.73 m² with a 95% confidence interval (CI) of -0.76 to 3.09 .

The limits of agreement are defined as mean ± 2 SD: 27.92 (95% CI: 24.56 to 31.24) and -25.59 (95% CI: -22.24 to -28.92) ml/min./1.73 m². This shows that the interval of both limits of agreement is not clinically



TABLE 1

Patient characteristics.

Patients, n	185
Mean age \pm SD, years	62 ± 11
Female, n (%)	105 (57)
Male, n (%)	80 (43)
Mean mGFR \pm SD, ml/min./1.73 m ²	85.12 ± 20.31
Mean creatinine, mmol/l	73
Mean eGFR by CKD-EPI, ml/min./1.73 m ²	86.29 ± 17.04
Mean BMI, kg/m ²	24.2
Mean BSA, m ²	1.78 ± 0.20
Cancer pulmonum, n (%)	143 (77.3)
Cancer ovarii, n (%)	28 (15.1)
Cancer testis, n (%)	8 (4.3)
Haematological cancer, n (%)	3 (1.6)
Cancer coli, n (%)	2 (1.1)
Breast cancer, n (%)	1 (0.5)

BMI = body mass index; BSA = body surface area; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; mGFR = measured glomerular filtration rate; SD = standard deviation.



TABLE 2

Bias, precision, inter-quartile range (IQR) and accuracy of Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations.

	n	Difference, ml/min./1.73 m ²			30% accuracy, %
		bias	precision	IQR	
MDRD	185	0.81 (-1.56 to 3.19)	16.49	20.63	88.64
CKD-EPI	185	1.16 (-0.76 to 3.09)	13.37	18.15	89.73

acceptable because the variation in differences may indicate discrepancies between both methods. This may be of clinical relevance, especially in those cases where GFR is below 85ml/min./1.73 m² as shown in the Bland-Altman plot (**Figure 1**).

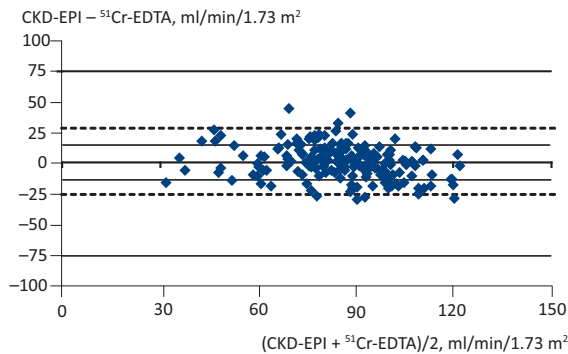
Bias, precision and accuracy results of eGFR with CKD-EPI equation (**Table 2**): The present study reports a mean *measured* GFR of 85.12 ± 20.31 ml/min./1.73 m² and a mean *estimated* GFR of 86.29 ± 17.04 ml/min./1.73 m² (32.84 to 134.56 ml/min./1.73 m².) based on the CKD-EPI formula. The bias based on mean difference is 1.16 (-0.76 to 3.09) ml/min./1.73 m² and inter-quartile range (IQR) of the differences of 18.15. Precision was 13.37 and accuracy within 30% (P30) was 89.73% versus 84.1% in the original study.

Validation of Chronic Kidney Disease Epidemiology Collaboration as a diagnostic test: Only 17 patients had an mGFR < 60 ml/min./1.73 m², which corresponds to a prevalence of 9%.

The positive likelihood ratio of CKD was 39.53 (95% CI: 12.36-26.43) and, consequently, a positive test in-


FIGURE 1

A Bland-Altman plot of the differences between estimated glomerular filtration rate (GFR) from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula and measured GFR by ⁵¹Cr-EDTA clearance in 185 patients showing the limits of agreement, precision and bias. The dashed lines represent the lines of agreement; the most solid line represents the mean difference between estimated and measured GFR or bias. The other two solid lines represent precision.



creased the post-test probability from 9% to 79.63%. Conversely, the negative likelihood ratio was 0.3 (95% CI: 0.14-0.63) and a negative test thus reduced the post-test probability from 9% to 2.88%.

Accuracy was 96%, defined as the proportion of all tests that would have yielded the correct result in a contingency table (**Table 3**).

DISCUSSION

Whenever a new screening method is validated against a gold standard, it is important to ascertain whether the differences in measurements between the methods are of clinical relevance or not.

In this study, eGFR was not significantly different from mGFR by ⁵¹Cr-EDTA (p value: 0.81), but there was considerable variation in the Bland-Altman plot as the limits of agreement were above 25 ml/min. This is clinically important. These two measurement methods therefore cannot be used interchangeably, at least not at values below 85 ml/min./1.73 m² because if no other parameters of kidney damage are used, a difference of

-25.59 ml/min./1.73 m² may imply a misclassification as CKD stage 3 [15].

The CKD stage determines which limits of agreement may be considered clinically relevant as a difference of only 15 ml/min./1.73 m² should give rise to much more concern in the interval between a GFR of 10 and 25 ml/min./1.73 m² than should a difference of 15 in the interval between a GFR of 100 and 115 ml/min./1.73 m² [16].

In 2005 Froissart et al [17] investigated a cohort of 2,095 adult Europeans. They used ⁵¹Cr-EDTA as a reference method and demonstrated that the imprecision of MDRD eGFR increased considerably at values above 60 ml/min./1.73 m² and for patients younger than 65 years. Although the sample size population of the two studies differed, they reported comparable levels of bias, precision and accuracy, even if the mean mGFR was highest in our study (85.12 versus 61.1 ml/min./1.73 m²).

Bias: 1.16 ml/min./1.73 m² versus -1 ml/min./1.73 m²; precision: 13.34 ml/min./1.73 m² versus 13.7 ml/min./1.73 m²; and accuracy within 30%: 89.73% versus 87.2%.

Due to the large variation in the estimates, it is important to consider measuring the GFR with a more reliable method whenever an accurate value of GFR is needed, as in patients for whom platinum-based treatment is planned.

We also acknowledge that a cancer population has pitfalls such as low muscular mass which will result in low creatinine levels. This may explain the differences between eGFR and mGFR, as plasma creatinine was measured up to three weeks before GFR. Patients with severe illness like cancer may display significant fluctuations in plasma creatinine in the interval between measurement of creatinine and ⁵¹Cr-EDTA. Still, the difference between the two plasma creatinine measurements was less than 15%. This is a potential source of error. The sample size was small, but sufficient power was obtained.

The CKD-EPI formula had a high specificity and a low sensitivity, but a low negative likelihood ratio of 0.30. This supports the claim that the test may be used as a screening tool in the general population whose risk

TABLE 3

Validation test results for Chronic Kidney Disease Epidemiology Collaboration and Modification of Diet in Renal Disease.

	Prevalence, %	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %	LR+	Pretest probability, %	Posttest probability, %
MDRD	9	76 (56-97)	96 (93-99)	65 (44-72)	98 (95-100)	94 (91-97)	18.35	9	64
CKD-EPI	9	71 (49-92)	98 (96-100)	80 (60-86)	97 (95-100)	96 (93-99)	39.53	9	80

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; LR+ = positive likelihood ratio; MDRD = Modification of Diet in Renal Disease; NPV = negative predictive value; PPV = positive predictive value.

of CKD is about 9-11%. However, the precise prevalence of CKD is unknown in cancer patients, wherefore MDRD may be a better choice because its negative predictive value is higher (98% versus 97%) and its negative likelihood ratio lower (0.25 versus 0.3). This may help us avoid overlooking patients with reduced GFR who may require a more accurate GFR measurement.

It remains unknown whether eGFR by means of the CKD-EPI or MDRD equation can detect minor changes in GFR during chemotherapy. Although a prospective longitudinal study would be required to settle this point, we are inclined to believe that eGFR would not be able to detect minor changes in accordance with the conclusions of a recent review [18].

CORRESPONDENCE: Belén Redal-Baigorri, Department of Nephrology, Roskilde Hospital, 4000 Roskilde, Denmark. E-mail: belenredal@hotmail.com

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CONFLICTS OF INTEREST: None

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