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Letter to the Editor

LETTER TO THE EDITOR

The non-steady state CKD-EPI calculator

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Formulas to estimate kidney function from rapidly changing plasma creatinine concentrations (pcr) have been available for many years [1–4]. Here, we present a method and provide an online calculator that estimates not only creatinine clearances but also glomerular filtration rate (GFR) in non-steady state conditions. Other defining features of our approach are the use of a full single pool, variable volume pharmacokinetic model [5] of creatinine and an integrated sensitivity analysis of its major determinants.

Our method is outlined in Figure 1. We use Equation (A) for creatinine clearance (crcl in mL/min).

Equation (A):

$$\mathrm{crcl} = -\frac{50\mathrm{deltavd}}{3t} + \frac{6250\mathrm{cgr}\left(-1+\left(\frac{\mathrm{deltavd}+\mathrm{vd1}}{\mathrm{vd1}}\right)^{\frac{60\mathrm{crclt}-1000\mathrm{vd1}+1000(\mathrm{deltavd}+\mathrm{vd1})}{1000\mathrm{deltavd}}}\right)}{9\left(-\mathrm{crea1}+\mathrm{crea2}\left(\frac{\mathrm{deltavd}+\mathrm{vd1}}{\mathrm{vd1}}\right)^{\frac{60\mathrm{crclt}-1000\mathrm{vd1}+1000(\mathrm{deltavd}+\mathrm{vd1})}{1000\mathrm{deltavd}}}\right)}.$$

It is calculated from two plasma creatinine measurements (crea1 and crea2 in umol/L), the time interval (t in h) between them, estimates of creatinine generation rate (cgr in mmol/day) and distribution volume (vd1 in L). Changes of the distribution volume (deltavd in L) during the time interval can also be taken into account. For situations without any changes in distribution volumes the formula simplifies to Equation (B) [2].

Equation (B):

$$\mathrm{crcl} = \frac{6250\mathrm{cgr}\left(-1+e^{\frac{3\mathrm{crclt}}{50\mathrm{vd1}}}\right)}{9\left(-\mathrm{crea1}+\mathrm{crea2}e^{\frac{3\mathrm{crclt}}{50\mathrm{vd1}}}\right)}.$$

Solving Equations (A) and (B) requires an iterative process and provides two possible solutions whenever the two creatinine measurements are not equal. One solution is the one we are interested in, the other represents the special situation where clearance is either zero for Equation (B) or equals the negative rate of change in distribution volume (i.e. $\mathrm{crcl} = \frac{-50\mathrm{deltavd}}{3t}$) for Equation (A). Because renal clearance is zero for both, we do not consider it further.

The conversion from non-steady state crcl to GFR is done as described by us before [6, 7]: under steady state conditions, crcl is given by creatinine excretion rate, which equals its generation rate, divided by the pcr. Using the crcl value derived from the non-steady state formula, we can thus calculate a corresponding, virtual steady state pcr (vsspcr in umol/L).

Equation (C):

$$\mathrm{vsspcr} = \frac{6250\mathrm{cgr}}{9\mathrm{crcl}}.$$

We then insert this virtual steady state pcr into Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and arrive at a body surface area normalized estimated GFR (eGFR) corresponding to the non-steady state crcl value.

To solve these complex calculations in clinical practice, we have constructed an online calculator (Figure 2 and Supplementary data, Items S2 and S3) with the software Mathematica, version 12.1.1.0 (Wolfram Research). It provides not only a non-steady state eGFR based on CKD-EPI, but also the non-steady state crcl and the virtual steady state pcr. Non-steady state eGFR results are given normalized to a body surface area (BSA) of 1.73 m^2 and in absolute, BSA-denormalized form (Figure 2A).

The calculations are done primarily with contemporary anthropometric estimates of creatinine generation rate [8] and distribution volume [9]. As their values have profound impact on the resulting kidney function, we demonstrate graphically the impact of deviations from these estimates (Figure 2B): we are showing non-steady state CKD-EPI results for creatinine

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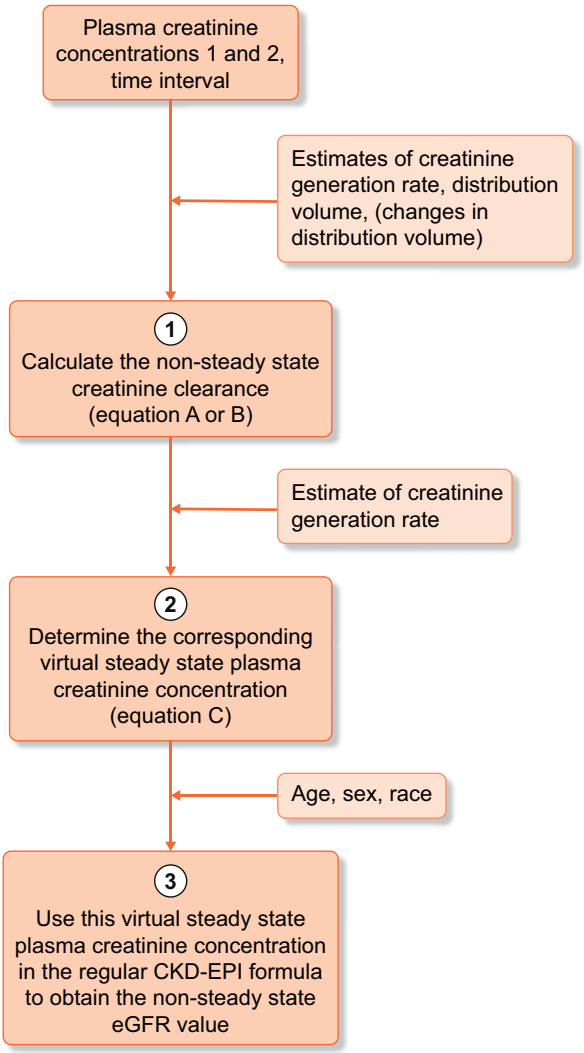

FIGURE 1: How to calculate non-steady state creatinine clearance and GFR.

generation rates differing ±3 and ±6 mmol/day from the calculated values, correlating roughly with one and two times the root mean square error (RMSE) of the underlying equation [8]. For distribution volume, we chose deviations of ±10 L, fitting two times the maximal RMSE [9]. The calculator also allows direct input of creatinine generation rate and distribution volume (Figure 2C). Default values are matched to recent population reference ranges [10], as described in Supplementary data, Item S3. Finally, change in distribution volume during the time interval can be inserted (Figure 2D), although its impact is generally small.

Our calculator provides a comprehensive, state-of-the-art estimation of non-steady state kidney function. Notable are the inclusion of a GFR estimation, the use of a full single-pool, variable volume pharmacokinetic model and contemporary anthropometric estimates of creatinine excretion rate and distribution volume with an integrated sensitivity analysis of their values and possible manual adaptations.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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FIGURE 2: Screenshot of the non-steady state CKD-EPI calculator. (**A**) Non-steady state kidney function estimates including BSA-normalized and -denormalized eGFR, creatinine clearance and virtual steady state plasma creatinine. (**B**) Influence of creatinine generation rate and distribution volume estimates on non-steady state eGFR. (**C**) Direct input of creatinine generation rate and distribution volume and corresponding non-steady state kidney function estimates. (**D**) Possible input of changes in distribution volume during the time interval.

AUTHORS' CONTRIBUTIONS

F.B. was responsible for the research idea and realization. S.S. and A.B. provided supervision. Each author contributed important intellectual content during manuscript drafting and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

S.S. reports personal fees from Baxter, personal fees from Fresenius, personal fees from Peripal, other from Calciscon, personal fees from Versantis, outside the submitted work. F.B. and A.B. have nothing to disclose.

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