Review Article

Importance of Glomerular Filtration Rate Determination and its Role in Drug-Dose Adjustments with Special Reference to Oncology

Abstract

Glomerular filtration Rate (GFR) measured in steady state is the best marker of kidney function. Glomerular filtration rate can be determined using exogenous markers like inulin, iothalamate, or iohexol (mGFR), or estimated using endogenous markers like creatinine and cystatin C (eGFR). Several equations are available, CKD-EPI equation is the recommended equation as per current guidelines. CKD-EPI creatinine equation refit (without the race variable) – 2021, and CKD-EPI creatinine - cystatin C equation refit (without the race variable)-2021 are the most recent recommendations from the National Kidney Foundation and the American Society of Nephrology.

Dose modifications of many drugs are needed in kidney dysfunction. In chronic kidney disease, as the kidney function is stable, determination of GFR is more accurate and can be used to modify the drug doses. Since the kidney function is not stable in acute kidney injury, determination of GFR is more difficult and it is not accurate. This makes it difficult to use it for determining dose modifications of drugs. Therapeutic drug level monitoring, and adjusting the dose based on pharmacokinetics/pharmacodynamics knowledge of the drug could be helpful in such cases. In oncology, accurate GFR measurement is crucial for adjusting the doses of chemotherapeutic agents to avoid toxicity and ensure efficacy, as cancer patients often have compromised kidney function due to the disease or its treatment. In this manuscript, we review all these aspects to provide a comprehensive understanding of GFR measurement and its implications in drug-dose adjustments, with a particular focus on how accurate GFR assessment is essential for optimizing chemotherapy dosing in oncology patients to minimize toxicity and maximize therapeutic efficacy.

Frequently, medical professionals need to depend on online calculators to get the value of eGFR, as these equations can be complicated. Scientific calculators can be used too, but that is not a common practice in nephrology clinics. The authors have shown in this paper how to use Microsoft Excel to create personal calculators, so that eGFR may be calculated by medical professionals and dialysis staff even when internet is not available due to institutional policies or otherwise. The 'Appendix' section given at the end of the paper shows how to create these personal calculators in Microsoft excel. Calculators for CKD-EPI equations can also be developed in excel, however the calculations are more complex, so I prefer using the programming language python to develop these calculators. In this paper, the authors have shown only the excel based calculators for CG equation and MDRD-4 (re-expressed) equation.

Keywords: Glomerular filtration rate, kidney function assessment, acute kidney injury

Introduction

Measuring glomerular filtration rate (GFR) is consideredas the best marker of kidney function. This is because GFR not only gives an indication of the glomerular filtration function, but also of other functions of the kidney, for example tubular reabsorption, tubular secretion, endocrine and metabolic functions.[1,2]GFR can be determined by assessing the filtration or clearance of exogenous markers (measured GFR or mGFR) or by measuring levels of endogenous markers (estimated GFR or eGFR).[1]

While mGFR is the gold standard for determining GFR, the procedure for determining eGFR is easier, and can be done in ambulatory settings. The process of determining mGFR that is cumbersome, and difficult to do in ambulatory settings.

For determining eGFR, endogenous filtration markers like creatinine and cystatin C are used. Both these tests can have inter-laboratory variability due to different methods of testing. To reduce this inter-lab variability and to get more reliable results, standardized creatinine and standardized cystatin C results are now recommended. Several equations are available for estimating GFR. Acute kidney injury (AKI) is a common and serious complication in cancer patients, often resulting in worse prognosis, interruption of cancer treatment, and increased healthcare costs. Assessing GFR in AKI is difficult because the renal function is not stable. This paper discusses the commonly available equations for estimating eGFR, with special reference to oncology.Methods used to assess kidney function in AKI have also been discussed in this paper.

The 'Appendix' section given at the end of the paper shows how to create these personal calculators in Microsoft excel. In this paper, the authors have shown only the excel based calculators for CG equation and MDRD-4 (re-expressed) equation.

Renal reserve

In normal circumstances, when there are no offending agents or "stress" to renal cells, the kidneys have a "resting" glomerular filtration rate(GFR). When exposed to an offending agent (for example a heavy protein meal (meat), or IV amino acid infusion, or intake of oral amino acid preparation) the kidneys can increase their GFR to maintain homeostasis. This extra capacity of the kidneys to increase the GFR from "resting state" or baseline to maximum when exposed to an offending agent is called renal reserve. This change in renal filtration or GFR can be seen after a protein load (like after taking a heavy animal protein meal). The response (increase in GFR) to the protein load can be seen as early as 1 hour after the protein meal, and peaks at 2-2.5 hours after the protein meal.[3]

Earlier, it was hypothesized that in an event of renal injury, this unused renal reserve would be depleted first before any fall in GFR occurs.[3] Measuring functional renal reserve and monitoring it can help in assessing kidney function. The drop in this renal reserve during a renal injury could serve as an early indicator of renal damage.[3]However, it was found that this hypothesis was not completely true. The response (example to heavy protein meal) is not completely lost in disease, so it does not represent a true 'renal reserve'. Also, the response if not homogeneous- it is heterogeneous. The response can occur because of several stimuli using different mechanisms.[3]

Glomerular filtration rate (GFR): Measured (mGFR) and Estimated (eGFR)

*Measured GFR (mGFR):*GFR can't be directly measured, so it is difficult to know the exact or 'true' GFR. Methods followed in practice include measuring GFR by assessing the filtration or clearance of exogenous markers (measured GFR or mGFR) or by measuring levels of endogenous markers (estimated GFR or eGFR).[1] Ideal method of measuring GFR (mGFR) is through measuring urinary clearance of exogenous markers such as inulin, ^{99m}Tc-DTPA [Technetium-99m-diethylenetriaminepetaacetic acid], ^{51}Cr-EDTA [chromium-51 labeled ethylenediamine tetraacetic acid], ^{125}I-Iothalamate or Iohexol.[1,4,5] Intravenous administration of these agents is needed over prolonged periods, and blood and urine samples are collected at appropriate time intervals to measure the GFR.[4]Seegmiller, et al found in their

clinical research (sample population 150 patients) that GFR determined using iohexol was lower compared to that determined using iothamamate method.[6]They further found in the in-vitro dialysis experiments from plasma samples of 10 patients that iohexol is less filterable compared to iothalamate. The authors believe that it could be due to greater binding of iohexol to the plasma proteins.[6]These observations should be kept in mind while determining GFR.[6]

Measured GFR or mGFR using Dried Blood Spots: Measuring GFR is a cumbersome and time-consuming method and is difficult to do in ambulatory settings. A method of measuring GFR that can be completed in a shorter time, and can be done in a shorter time making it a possible solution in ambulatory settings is by measuring GFR by determining iohexol clearance using dried capillary blood spots (DBS).[7] GFR measured by iohexol clearance using DBS is comparable to GFR measured by plasma clearance of iohexol.[7]In this method, iohexol is injected using a peripheral IV line. Then, instead of collecting blood samples at regular time intervals (as required in plasma estimation of iohexol to measure plasma clearance), the patient needs to prick his fingers using a lancet (as done by diabetic patients to check blood sugar level) [this can be done at home by patient], and the dried blood spot is collected (on filter paper). The filter paper with DBS is sent to the lab for testing. The lab prepared punched out discs with the DBS in the disc and do the analysis to determine iohexol clearance.[7]

*Estimated GFR (eGFR):*Determining mGFRrequired a lot of efforts and is time consuming. It is difficult to do in ambulatory settings. Hence there has been a continuous effort to find a reasonably reliable endogenous marker (like creatinine, cystatin C) that does not need to be administered from outside (eGFR calculation).

Cystatin C is produced by all nucleated cells. Cystatin C based GFR calculations are independent of protein intake and muscle mass. If both cystatin C and creatinine are used to estimate GFR, it is more accurate.[4]

Several equations and nomograms have been developed in the past to help in assessing GFR with reasonable accuracy. Noteworthy equations are Cockcroft-Gault (CG) Equation, MDRD equation, and CKD-EPI equation.[4,5] For validating eGFR equations, Urinary iothalamate clearance and plasma clearance of iohexol are two widely practiced methods.[1,6]

Measurement of Serum Creatinine

The Jaffe reaction using alkaline picrate is the most common method for measuring serum creatinine.[2]In this reaction, the creatinine in the sample changes in the alkaline medium and responds with picric acid and turns into orange. This color change is measured to estimate the creatinine level.[8] Earlier, several factors could give rise to an overestimation of GFR through this method and included presence of protein, bilirubin, ascorbate, pyruvate, albumin, glucose, acetoacetate (formed during ketogenesis in diabetes mellitus), and cephalosporins. With the advances and improvement of the Jaffe reaction method, many such issues were resolved. For example, using Beckman Synchron CX3 analyzer, the temperature of the creatinine reaction cup was increased from 37 °C to 42 °C so that acetoacetate interference became minimal when the main creatinine reaction was checked at 25.6 seconds.[2]

The other commonly used methods are the 'Enzymatic' methods. They are more specific when compared to the Jaffe reaction, but they have their own problems, for example, interference from bilirubin and high creatinine levels in the samples causing an underestimation of creatinine.[2] With

advances in this method including the use a more efficient hydrogen peroxide acceptor (triiodo-hydroxy-benzoic acid), and the use of potassium ferrocyanide and detergents to reduce bilirubin interference, these methods have also become more accurate.[2,8]

Isotope dilution-liquid chromatography-mass spectrometry (IDLCMS): This method is the most accurate method, but is expensive.[8,9]

Nanotechnology (Nano-based methods) and Molecular Imprinting methods: These are other methods that can be used for determining serum creatinine levels.[8]

StandardizedCreatinine

Because of the variations that can occur because of different methods that can be used for determining creatinine levels, and because of inter-laboratory variations in the test results, standardizing the serum creatinine results from different labs became a priority. To be able to achieve this objective, National Kidney Disease Education Program (NKDEP) has recommended that all creatinine methods should become traceable to a reference method based on isotope dilution-mass spectrometry (IDMS).[2,10]

Measurement of serum cystatin C

Given below are some of the methods that can be used to measure serum cystatin levels:

- Genzyme cystatin C immunoassay.[11]
- Enzyme linked immunosorbent assay (ELISA).[12]
- Particle- enhanced Immunoturbidimetric method (PETIA).[13]
- Latex particle-enhanced nephelometric immunoassay (PENIA)[14]

Measurement of cystatin C costs more than serum creatinine, is not widely available, takes more time in getting the test results.[15,16]Further, the costs of these tests differ at different places.

Standardizedcystatin C

Standardized cystatin C values are traceable to the results from International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and/or Institute for Reference Materials and Measurements (IRMM) working group.[10]

Equations for Calculating eGFR

Several equations have been developed to estimate GFR. These equations are helpful when kidney function is reasonably stable- so they are helpful in healthy individuals and in chronic kidney disease (conditions in which we don't see much fluctuation in renal function).[17]These equations ignore renal functional reserve.[3,17]

Cockcroft-Gault (CG) Equation

Donald Cockcroft and his mentor Henry Gault developed the Cockcroft-Gault (CG) Equation in 1973. This began as a simple research project to evaluate the accuracy of a creatinine clearance nomogram proposed by Siersbaek-Nielsen in 1971.[18]The equation uses creatinine clearance as an estimate of GFR. This equation to calculate eGFR has been widely used because of its simplicity and ease. The equation is given below:

$$\text{Creatinine Clearance} = \left[\frac{(140 - \text{age}) \times \text{weight of the person}}{72 \times \text{serum creatinine}}\right] \times 0.85 \text{ (if female)}$$

Age in years
Creatinine clearance in ml/min
Weight in kilograms (Kg)
Serum creatinine in mg/dl

However, this equation requires the renal function to be in steady state. Additionally, it can be inaccurate in situations where there is significant obesity or significant fluid retention when, according to Cockcroft, the ideal weight should probably be used. Another point to note is that the equation is suitable for individuals with normal muscle mass and function. It could be inaccurate in individuals with significant muscle disease, including muscle wasting.[18]It is not adjusted for body surface area.[19]

The National Kidney Foundation recommends not to use this equation to calculate eGFR as this equation has not been expressed using standardized creatinine values.[19]

Modification of Diet in Renal Disease (MDRD) equations

Andrew S Levey, et al, in their study on 1628 patients, found that MDRD equation estimated eGFR more accurately as compared to Cockcroft-Gault (CG) Equation.[20]The original Modification of Diet in Renal Disease (MDRD) equation has 6 variables (MDRD 6). The variables areage, sex, ethnicity, serum creatinine, urea, and albumin. Later, the MDRD 6 was modified and simplified to a 4-variable version (MDRD-4). In MRDR 4, the variables are: age, sex, ethnicity, and serum creatinine.[20,21]

Now, this MDRD 4 has further been modified or re-expressed by using standardized serum creatinine.[21]

MDRD 6-variable equation (MDRD6)[22]

MDRD 6 variable equation (MDRD6), eGFR in ml/min/1.73m^2= 198 × [serum creatinine(mg/dL)]$^{-0.858}$ × [age]$^{-0.167}$ × [0.822 if patient is female] × [1.178 if patient is black] × [serum urea nitrogen concentration (mg/dL)]$^{-0.293}$ × [urine urea nitrogen excretion (g/d)]$^{0.249}$

MDRD 6-variable equation (MDRD7)[20,22]

MDRD 6 variable equation(MDRD7), eGFR in ml/min/1.73m^2= 170 × (Scr)$^{-0.999}$ × (Age in years)$^{-0.176}$ × (0.762 if female) × (1.180 if black) × (SUN)$^{-0.170}$ × (A)$^{0.318}$

Abbreviations:

- Scr= serum creatinine (mg/dL)
- SUN is serum urea nitrogen concentration (mg/dL)
- A=Albumin in g/dl

MDRD 4 variable equation[23,24]

eGFR in mL/min/1.73 m^2 = 186 × (Scr)$^{-1.154}$ × (Age in years)$^{-0.203}$ × (0.742 if female) × (1.212 if ethnicity is black)

Abbreviation: Scr= serum creatinine (mg/dL).

MDRD 4 variable equation (re-expressed)[20,25,26]

eGFR in mL/min/1.73 m^2= 175 x standardized $Scr^{-1.154}$ x (age in years)$^{-0.203}$ x 1.212 (if ethnicity black) x 0.742 (if female)

Abbreviations: Scr= serum creatinine (mg/dL).

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations

- **CKD-EPI creatinine (2009)**[27,28]

eGFR = 141 x min(Scr/K,1)$^{\alpha}$ x max(Scr/K,1)$^{-1.209}$ x $0.993^{\text{age in years}}$ x 1.018 [if female] x 1.159 (if black ethnicity)

Abbreviations:

- Scr = serum creatinine in mg/dL
- K = 0.7 (females) or 0.9 (males)
- α = -0.329 (females) or -0.411(males)
- min = the minimum of Scr/K or 1
- max = the maximum of Scr/K or 1

- **CKD-EPI cystatin C (2012)**[29,30,31]

eGFR in mL/min/1.73 m^2= 133 × min(Scys/0.8, 1)$^{-0.499}$ × max (Scys/0.8, 1)$^{-1.328}$ × 0.996^{Age} [× 0.932 if female]

Abbreviations:

- Scys is serum cystatin C
- min indicates the minimum of Scr/κ or 1
- max indicates the maximum of Scys/κ or 1

Cystatin C is not affected by muscle mass.[30,32] Additionally, it is not significantly affected by diet.[30] This brings forth the speculation that cystatin C based equations should be more accurate in estimating eGFR than creatinine-based equations. However, this has not been found true in practice, indicating that some unmeasured factors may be affecting eGFR determination with Cystatin C as a lone filtration marker.[30]Other attractive points in favor of cystatin C when compared with creatinine are that cystatin C is less affected by age, race, and gender. Lesley A Inker et al found in their study that addition of race in cystatin C based equation did not have a significant impact on estimated eGFR. The authors further propose that given that occasionally it is difficult to assign a race, and frequently when analyzing a sample in a lab the details of race are not available, having eGFR based on a filtration marker that does not depend on race, or having equations that don't have race as a variable could be useful both in clinical practice and in research.[30]

CKD-EPI creatinine – cystatin C (2012)[30,31]

eGFR in mL/min/1.73 m^2= 135 × min(Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-0.601}$ × min(Scys/0.8, 1)$^{-0.375}$ × max(Scys/0.8, 1)$^{-0.711}$ × 0.995^{Age} [× 0.969 if female] [× 1.08 if black]

Abbreviations:

- Scr: serum creatinine
- Scys: serum cystatin C
- κ: 0.7 for females and 0.9 for males
- α: −0.248 for females and −0.207 for males
- min: the minimum of Scr/κ or 1
- max: the maximum of Scr/κ or 1

The creatinine-cystatin equation has been found to be better than the equations based on creatinine alone or cystatin alone.[30]

Recent Recommendations

A task force was organized by the National Kidney Foundation and the American Society of Nephrology in 2020 to re-evaluate the inclusion of race in the equations used for measuring eGFR. The task force, after 10 months of evaluation (from September 2020 to June 2021), recommended that for US adults, CKD-EPIcr_R without the race variable should be implemented immediately for evaluations of eGFR. The taskforce also recommended timely use of cystatin C for to confirm eGFR in adults with CKD or at risk of CKD because the combined filtration marker of cystatin C and creatinine is more accurate in assessing eGFR. They further recommended that CKD-EPI eGFR–cystatin C (eGFRcys) and eGFR creatinine–cystatin C (eGFRcr-cys_R) refit without the race variables should be adopted for estimation of eGFR.[15]

CKD-EPI creatinine equation refit (without the race variable) (CKD-EPIcr_R) (2021): This equation relies entirely on serum creatinine estimation.[15]The equation is given below[33,34]

$$eGFR(mL/min/1.73\ m^2) = 142 \times \min(Scr/K,1)^{\alpha} \times \max(Scr/K,1)^{-1.200} \times 0.9938^{\text{age in years}} \times 1.012 \text{ [if female]}$$

Abbreviations:

- Scr = standardized serum creatinine in mg/dL
- K = 0.7 (females) or 0.9 (males)
- α = -0.241 (females) or -0.302 (males)
- min = the minimum of Scr/K or 1
- max = the maximum of Scr/K or 1

CKD-EPI creatinine - cystatin C equation refit (without the race variable) (CKD-EPIcr-cys_R) (2021): This equation uses both serum creatinine and cystatin C measurements.[15,31] This equation is more accurate than CKD-EPIcr_R equation.

$$eGFR\ (mL/min/1.73\ m^2) = 135 \times \min\ (Scr\ /\kappa,\ 1)^{\alpha} \times \max\ (Scr\ /\kappa,\ 1)^{-0.544} \times \min\ (Scys/\ 0.8,\ 1)^{-0.323} \times \max\ (Scys/\ 0.8,\ 1)^{-0.778} \times 0.9961^{Age} \times 0.963 \text{ [if female]}$$

where:

- Scr = standardized serum creatinine in mg/dL
- Scys = standardized serum Cystatin C

- κ = 0.7 for females and 0.9 for males
- α = -0.219 for females and -0.144 for males
- min = the minimum of Scr /κ or 1
- max = the maximum of Scr /κ or 1

Dose Adjustment of Drugs in Renal Impairment

As pointed out by Smith, small changes in serum creatinine represent large changes in GFR when renal function is normal or only mildly impaired.[35]In patients with renal impairment, the dose of renally excreted drugs should be reduced in proportion with the reduction in glomerular filtration, making it necessary to measure or estimate the GFR to make appropriate dose adjustments.[35]

In renal impairment, because of lower clearance, adverse effects and toxicitycould occur due to higher systemic exposure of the drugs.[36]The dose adjustments need to be very carefully monitored in drugs that have low therapeutic index (therapeutic index = minimum toxic dose/minimum effective dose).[37,38] Examples of the drugs with low therapeutic index include, but are not limited to, aminoglycosides (amikacin, gentamycin), vancomycin, digoxin, lithium, warfarin, anticonvulsants (lamotrigine, phenytoin), amiodarone, thyroxine, insulin, and tacrolimus.[37]The effect and toxicity of the drug should be carefully monitored. Therapeutic drug level monitoring is recommended for these drugs with low therapeutic range or narrow therapeutic index.[39]

The dose adjustment is done based on the GFR levels. Previously, Cockcroft-Gault equation was commonly used. Later, MDRD equations were found to be more accurate in predicting eGFR and were used for eGFR calculations and adjusting the dose of drugs. CKD-EPI equations, that came later, showed even better eGFR determination, and are being used for dose determination of drugs in renal impairment. Use of standardized serum creatinine and/or Cystatin C values are recommended for the eGFR determination, as these values minimize inter-laboratory variations in the levels and are more accurate.[2,10,15,33,34]Currently, CKD-EPI equations are more commonly used, and "have largely replaced" MDRD and Cockcroft-Gault equations.[36]

Recently, in 2021, the task force organized by National Kidney Foundation and American Society of Nephrology recommended removal of race from the CKD-EPI formulae, as it was found that the race variable in the equations did not have significant impact on the eGFR determination. Currently, these equations are recommended for calculating eGFR and for dose adjustment of drugs that need adjustments in renal impairment.[15]

Body surface area (BSA) standardized eGFR values (unit: ml/min/1.73m^2) may not be appropriate in very large (underestimated GFR) or very small (overestimates GFR) patients. This could be a problem when calculating the dose for these patients, especially of drugs with narrow therapeutic indices. US National Institute of Health (NIH) guidelines say that for these patients, eGFR (Body Surface Area indexed value) should be multiplied by the BSA of the patient and divided by 1.73m^2 to obtain eGFR (absolute value) in ml/min, and this eGFR should be used for drug dose adjustments.[40,41]

> eGFR (in absolute value, ml/min) = eGFR (BSA indexed value, ml/min/1.73m^2) x Patient's body surface area/1.73m^2

Drug dose adjustment guidelines in acute kidney injury are difficult and challenging. The equations available to estimate GFR are all based on stable serum levels of the endogenous markers (creatinine,

cystatin C). These equations may give unreliable estimate of GFR in acute kidney injury. KDIGO guidelines have mentioned a reasonable strategy to determine GFR in AKI. The strategy involves measuring the endogenous marker levels (i.e., creatinine) at the beginning and end of a pre-specified period, and calculating the mean of these values, and use the mean to determine the eGFR. A shorter time-period than 24 hours has been recommended in KDIGO guidelines for patients with rapidly changing renal functions. The guidelines mention, however, that it is near impossible to provide a guidance regarding best dosage regimen in critically ill patients with multiple organ dysfunction, or multiple organ failure.[42]

In many cases, the fist dose that is given to a patient with AKI is the same as that in people with normal renal function. Sometimes it the first dose may be higher as the volume of distribution is frequently higher in sepsis, multi-organ dysfunction or multi-organ failure, including AKI. This is followed by lower maintenance doses, and further adjustments can be done by PK/PD assessments and therapeutic drug monitoring.[42,43]

The principles that guide drug dose adjustments in CKD guide dose adjustments in AKI as well. Principles of pharmacokinetics like absorption, volume of distribution, metabolism, and elimination may help in optimizing and guiding therapy. Pharmacokinetics (PK) and pharmacodynamics (PD) monitoring approach should be used, especially for drugs with narrow therapeutic range. When the pharmacokinetics are not clear, a "start low and go slow" approach has been recommended.[43] Therapeutic drug monitoring is recommended in these situations.[42]

Adjusting the Anticancer Drug Dose in Kidney Dysfunction

Patients with CKD, especially those on dialysis, or post kidney transplantation, are at higher risk of developing malignancies. About 12-25% of cancer patients are found to be having kidney dysfunction at dose initiation.[38]Janus N, et al included 1218 patients in their study and found that 78.6% of the patients needed at least one drug that needed dose adjustment, and 78.1% of the patients received at least 1 nephrotoxic drug.[38,44]

Anticancer Drug Dosing in Kidney Dysfunction (ADDKID) guidelines recommend the use of CKD-EPI for determining eGFR, except in situations where directly assessing GFR using mGFR is necessary. [38]ADDKID recommends assessing GFR as close as possible to the time of administering the anti-cancer drug.[38]

ADDKID guidelines say that mGFR is preferred to guide the initial dosing of certain anti-neoplastic drugs, including, but not limited to, carboplatin, cisplatin, and high dose methotrexate (≥500mg/m^2).[38,45]mGFR is also preferred to guide initial dosing in conditions including (but not limited to) patients with extremes of body size or muscle mass, patients with amputation, or paraplegia.[38]

ADDKID guidelines have discussed dose adjustments in several drugs including azacitidine, bendamustine, bevacizumab, bleomycin, bortezomib, carboplatin, cisplatin, dacarbazine, doxorubicin and others.[38]The guidelines can be accessed from the link below:

> ADDKID Guidelines: https://www.eviq.org.au/getmedia/b33e4b06-cc18-4cd9-9d0f-3826530c6c53/ADDIKD-Guideline-2022.pdf

Adjusting drug dosage in CKD versus AKI settings

Adjusting the dose of drugs in CKD is relatively easy compared to that in acute kidney injury (AKI) because the eGFR calculations shown above rely on stable kidney function that is seen in CKD. In AKI, the renal functions are not stable, so the eGFR calculated based on the above equations could be erroneous, and special precautions need to be taken to be able to adjust the dose of medicines with reasonably acceptable precision. Before we dive in the complexities that are involved in calculating eGFR and adjusting drug dosage in AKI, let us look at the three AKI classification criteria that are widely used in nephrology and intensive care settings. The three AKI classification criteria are RIFLE criteria, AKIN criteria, and KDIGO criteria and these are discussed below.

Classification of Acute Kidney Injury (AKI)

The three most commonly used criteria for defining and classifying acute kidney injury include:

- **RIFLE Criteria**[Risk, Injury, Failure, Loss, and End Stage]: Acute Dialysis Quality Initiative developed the RIFLE criteria in 2004.[46,47]This criterion classifies AKI into three grades of severity: Risk, Injury, and failure.[46,48]
  The table below (Table 1) provides the details of these grades of severity.[46,47,48]

Table 1: RIFLE Criteria for classifying AKI		
Grade	**Serum creatinine Criteria**	**Urine Output Criteria**
Risk	Rise in serum creatinine ≥1.5 times baseline or decrease in GFR ≥25%	Less than 0.5 mL/kg/h for ≥6 h
Injury	Rise in serum creatinine ≥2.0 times baseline or decrease in GFR ≥50%	Less than 0.5 mL/kg/h for ≥12 h
Failure	Rise in serum creatinine ≥3.0timesbaseline or decrease in GFR ≥75% or an absolute serum creatinine ≥354 µmol/L with an acute rise of at least 44 µmol/L	Less than 0.3 mL/kg/h ≥24 h or anuria ≥12 h

- **AKIN Criteria** [Acute Kidney Injury Network]: In 2007, the Acute Kidney Injury Network (AKIN) proposed a modification of RIFLE criteria. The modifications aimed to increase sensitivity of identifying AKI by decreasing the serum creatinine threshold and placing patients on renal replacement therapy in stage 3.[46, 48]The details of the stages are given below in table 2.[46,48]

Table 2: AKIN Criteria for classifying AKI		
Stage	**Serum creatinine Criteria**	**Urine Output Criteria**
1	Rise in serum creatinine ≥26.2 µmol/L or increase to ≥150–199% (1.5- to 1.9-fold) from baseline	<0.5 mL/kg/h for ≥6 h
2	Rise in serum creatinine to 200–299% (>2–2.9 fold) from baseline	<0.5 mL/kg/h for ≥12 h
3	Rise in serum creatinine to ≥300% (≥3-fold) from baseline or serum creatinine ≥354 µmol/L with an acute rise of at	<0.3 mL/kg/h ≥24 h or anuria ≥12 h

	least 44 µmol/L or initiation of RRT	

- **KDIGO Criteria** [Kidney Disease: Improving Global Outcomes]:KDIGO published guidelines for classifying AKI in 2012.[49] These guidelines are given below in table 3.[49]

Table 3: KDIGO Criteria for classifying AKI		
Stage	**Serum creatinine Criteria**	**Urine Output Criteria**
1	1.5–1.9times baseline OR increase of ≥0.3 mg/dl (≥26.5 mmol/l)	Less than 0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	Less than 0.5 ml/kg/h for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 mmol/l) OR Initiation of renal replacement therapy OR, in patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	Less than0.3 ml/kg/h for ≥24 hours OR Anuria for ≥12 hours

Biomarkers and innovative technologies for early detection of AKI

The quest continues for novel biomarkers and innovative technologies to help in early identification of AKI, or to indicate prognosis.[50]Several biomarkers including N-acetyl-β-glucosaminidase (NAG), β2-microglobulin, α1-microglobulin, Kidney Injury Molecule-1 (KIM-1), Neutrophil Gelatinase-Associated Lipocalin (NGAL), Interleukin-18, have been studied and proposed as potential biomarkers for early detection of AKI.[50]They all have their strengths and pitfalls. Innovations in technology are also coming up, for example nanotechnology as a tool for diagnosis and treatment of AKI, and development of probes like 'Near-infrared fluorescence imaging probe'.

Acute Kidney Injury in cancer patients

There are key risk factors for AKI in cancer patients including older age, pre-existing chronic kidney disease, diabetes, volume depletion, and the use of nephrotoxic medications.[51,52,53] Identifying these risk factors is crucial for early intervention and prevention.[51,52,53]AKI in cancer patients be prerenal, renal or post-renal. The causes include tumor lysis syndrome, malignant infiltration, urinary tract obstruction (for example, due to external compression from a lymph node or the tumor), sepsis, radiotherapy, nephrotoxic drugs (including cisplatin, mitomycin-C, gemcitabine, methotrexate, ifosfamide and pemetrexed).[53,54]The diagnostic approach to AKI in cancer patients involves a thorough assessment of patient history, physical examination, and laboratory tests. Imaging studies such as ultrasound or CT scans may be necessary to identify obstructive causes of AKI.[53] A kidney biopsy can be considered in cases where the diagnosis is unclear or when specific treatment decisions depend on histological findings.[51,52]

In cancer patients, AKI could indicate worse prognosis. Development of AKI can result in withdrawal from effective oncological treatments, longer hospitalizations and increased costs.[53] 4The incidence of AKI in cancer patients varies widely, with studies reporting rates from 17.5% to 56% depending on the type and stage of cancer, treatment regimen, and patient comorbidities.[53,55] Renal cell carcinoma,

multiple myeloma (common cause being cast nephropathy), liver cancer, and leukemia are most commonly associated with development of AKI.[53]

Determining the GFR in cancer patients before starting anticancer treatment is crucial for several reasons, one being many of these drugs have narrow therapeutic index.[56] Accurate GFR assessment helps to determine the appropriate dosage of anticancer drugs, ensuring they are both effective and safe. Many anticancer drugs are excreted through the kidneys, and incorrect dosing can lead to either undertreatment or severe toxicity.[56] Cancer patients often have pre-existing CKD or are at risk of developing AKI during treatment.[52,53,54] Monitoring GFR helps in identifying these risks early and managing them effectively. Knowing the GFR allows healthcare providers to tailor treatment plans, including the selection of drugs and supportive care measures, to minimize renal damage and other side effects.[56] Regular GFR monitoring throughout the treatment course is essential for adjusting medication dosages as required and for promptly identifying any decline in kidney function.[56]

Cancer specific GFR estimation methods

Some investigators have created drug dosing equations based on mGFRbecause accurate measurement of GFR and drug dose calculation is critical for cancer patients. Martin formula and the Wright formula use[51]Cr-EDTA plasma clearance concentrations to determine GFR. Calvert formula uses GFR as a measure of drug clearance, and overall systemic plasma drug concentrations (Area under curve or AUC) and target AUC to determine drug dose.[56] Calculation of carboplatin dosing using Calvert formula is recommended by the National Comprehensive Cancer Network, for carboplatin dosing based on specific AUC targets (such as 4–6 mg/ml per minute).[56]

GFR Assessment in Real Time

FAST BioMedical methodology for GFR determination measures GFR and plasma volume in real time by using fluorescent markers and fluorometer to detect fluorescence.[56]MediBeacon transdermal GFR measurement system uses a small light sensor on patient's skin that detects fluorescence, a biocompatible fluorescent tracer (MB-102 or relmapirazin) that is injected in the patient, and a monitor that displays the results.[56]

Conclusion

Glomerular filtration rate can be determined using exogenous markers like inulin, ^{99m}Tc-DTPA [Technetium-99m-diethylenetriaminepetaacetic acid], ^{51}Cr-EDTA [chromium-51 labeled ethylenediamine tetraacetic acid], iothalamate, or iohexol (mGFR), or estimated using endogenous markers like creatinine and cystatin C (eGFR). Several equations are available, including Cockcroft-Gault equation, MDRD equations, and CKD-EPI equations. CKD-EPI equation is the recommended equation as per current guidelines. CKD-EPI re-expressed equation using both creatinine and cystatin as variables (without race as a parameter) gives the most accurate results compared to all other equations currently available. Current recommendation is to use CKD-EPI-creatinine (re-expressed) 2021 equation for estimating eGFR, and CKD-EPI-creatinine-cystatin (re-expressed) 2021 equation for a more accurate result when needed.[60]

Measuring creatinine levels and cystatin C levels can be done through several methods. The results could vary based on the method used, and there could occur inter-laboratory variations in the results.

The guidelines suggest using standardized creatinine and cystatin C levels to get a more accurate estimate of eGFR.

Cancer patients are at higher risk of developing acute kidney injury (AKI). The risk of AKI has been found to be highest in patients with multiple myeloma, leukemia, and bladder cancer.[57]Several factors can contribute to development of AKI, the causes include (but are not limited to) drug-induced, sepsis, hypovolemia, tumor lysis syndrome, outflow tract obstruction, and urinary tract infections.[38,58] About 27% of the cancer patients can develop acute kidney injury (AKI) during treatment.[59]Seven to 10% of the cancer patients could need renal replacement therapy.[38]

Dose modifications of many drugs are needed in kidney dysfunction. In chronic kidney disease, as the kidney function is stable, determination of GFR is more accurate and can be used to modify the drug doses. Since the kidney function is not stable in acute kidney injury, determination of GFR is more difficult and it is not accurate. This makes it difficult to use it for determining dose modifications of drugs. Therapeutic drug level monitoring, and adjusting the dose based on pharmacokinetics/pharmacodynamics knowledge of the drug could be helpful in such cases.

Assessing renal function before beginning anticancer treatment is vital because it guarantees accurate drug dosing, as many medications are excreted via the kidneys. This ensures that patients receive the appropriate treatment dosages, avoiding both undertreatment and severe toxicity. Additionally, it helps to identify patients at risk of AKI or those with pre-existing CKD, allowing for tailored treatment plans that minimize renal damage and other side effects. Regular monitoring of renal function throughout treatment is essential to adjust dosages as needed and promptly detect any decline in kidney function. ADDKID (Anticancer Drug Dosing in Kidney Dysfunction) have given a very comprehensive overview of cancer drugs dose adjustment. KDIGO guidelines also give a very detailed overview of how to adjust the doses of drugs in renal impairment, including that in acute kidney injury.

The research and hunt for newer ways to diagnose and treat kidney diseases continues. Newer probes, applications of nanotechnology, exploring other biomarkers, and recently the application of artificial intelligence is being witnessed by the scientific community. The scientific quest is aggressive, and this is nothing less than exciting.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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APPENDIX

Creating personal eGFR calculators in Microsoft excel

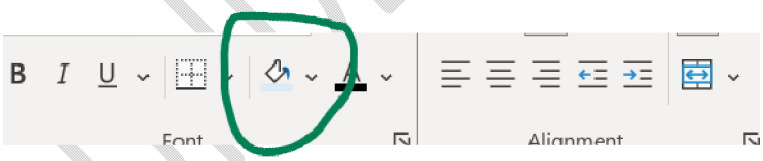
Calculator 1: Microsoft Excel based eGFR calculator using CG equation

A snapshot of the calculator is shown below:

eGFR calculator: Cockcroft-Gault equation						
Age in years	Weight in Kg	Serum Creatinine in mg/dl	Sex (1 if female, 0 if male)	calcM	calcF	Creatinine clearance in ml/min
60	50	3	0	18.51851852	15.7407407	18.51851852

Now, how to make it? Follow the steps given below:

Open your Microsoft excel, and in your sheet type the following in the cells (rows and columns) mentioned. For example, the heading 'Age in years' should be in C3 cell (C column and 3rd row). Colour the cells as shown in the snapshot below. Just select the cells you want to colour, and click on the shading tool, or the paint-bucket (shown below), and select your colour.



eGFR calculator: Cockcroft-Gault equation						
Age in years	Weight in Kg	Serum Creatinine in mg/dl	Sex (1 if female, 0 if male)	calcM	calcF	Creatinine clearance in ml/min

The title 'eGFR calculator: Cockcroft-Gault equation' should be types in the cell C2. Then select cells from C2 through I2, and go up and click the merge tool shown below.

Once done, it is time to enter the formulae. The letters (A,B,C,D…) in the excel sheet shown on the top indicate columns, and the numbers (1,2,3,4..) shown on extreme left indicate rows. So, A2 is A column, 2nd row; I4 is I column, 4th row.

Now, in calcM column, in G4 cell, enter the following formula:

=((140-C4)*D4/(72*E4))

Press enter.

Next, in calcF column, in H4 cell, enter the following formula:

=((140-C4)*D4/(72*E4)*0.85)

Press enter.

Now, it is time for the last one. In 'Creatinine clearance in ml/min' column, in I4 cell, enter the following formula:

=IF(F4=1,H4,G4)

Press enter.

That's it! Your calculator is ready. As you have not yet entered any data in the calculator, the cells G4,H4 and I4 may show '#DIV/0!' value. Don't worry about it. Just enter the patient's data in the blue shaded cells, and the whole thing works.

Enter the values of your patient in 4th row from C to F columns (the blue shaded cells) and get your creatinine clearance in ml/minute in the 'I4' cell (the grey shaded cell).

Calculator 2:Microsoft Excel based eGFR calculator using MDRD 4 variable equation (Re-Expressed)

Create the design of the calculator as shown below:

	A	B	C	D	E	F	G	H	I	J	K	L	M
1													
2			eGFR calculator: MDRD-4 (re-expressed)										
3			Standardized serum creatinine in mg/dl	Age in years	Sex: 1 for female, 0 for male	Race: 1 for 'black', 0 for others	calc1	Sex_0_Race_0	Sex_0_Race_1	Sex_1_Race_0	Sex_1_Race_1	eGFR in ml/min/1.73m2	
4													
5													

Now, in cell G4, type the following formula:

=175*(C4^-1.154)*(D4^-0.203)

Press enter.

In cell H4, type the formula given below:

=IF(AND(E4=0,F4=0),G4,0)

Press enter.

Now, in cell I4, type the following formula:

=IF(AND(E4=0,F4=1),G4*1.212,0)

Press enter.

Now, in cell J4, type the formula:

=IF(AND(E4=1,F4=0),G4*0.742,0)

Press enter.

Again, in cell K4, type the formula:

=IF(AND(E4=1,F4=1),G4*0.742*1.212,0)

Press enter.

Now, in cell L4, type the formula:

=MAX(H4:K4)

Press enter.

The calculator is ready now. Enter the patient's data in the blue shaded cells (C4 to F4), and press enter. The eGFR is displayed in the grey shaded cell L4.

The result of the calculator is shown in the snapshot below. Hypothetical values have been entered in the cells C to F4:

eGFR calculator: MDRD-4 (re-expressed)									
Standardized serum creatinine in mg/dl	Age in years	Sex: 1 for female, 0 for male	Race: 1 for 'black', 0 for others	calc1	Sex_0_Race_0	Sex_0_Race_1	Sex_1_Race_0	Sex_1_Race_1	eGFR in ml/min/1.73m2
4	56	1	1	15.60913	0	0	0	14.0373515	14.03735148