Formulae for estimation of kidney function as an approach to calculating drug doses: A scoping review

Arba Pramundita Ramadani, Sekawanti Fuji Kartika, Vitarani Dwi Ananda Ningrum
1 Department of Pharmacy, Universitas Islam Indonesia, Yogyakarta, Indonesia
2 Pharmacist Professional Study Programme, Universitas Islam Indonesia, Yogyakarta, Indonesia

Keywords
Drug safety
Estimation formula
Kidney function

Abstract
Background: The kidneys are the main organ for drug excretion, and it is critical to assess kidney function when designing dosage regimens for drugs that undergo renal elimination. Various formulae have been used to estimate kidney function and safely adjust doses. Objective: This research reviewed studies that assessed patients' kidney function with various approaches to provide appropriate choices of kidney function estimation formulas based on patients' age and clinical conditions. Method: The search involved browsing scientific articles in PubMed and ScienceDirect with the keywords ("assessment" AND ("GFR" AND ("formula") OR ("renal function") AND ("human")) AND ("Creatinine" OR "creatinine")). The articles included were those available in full text and English. Thirty articles addressing the formulae for kidney function assessment were reviewed. Result: The Schwartz formula is more appropriate for pediatric and adult patients, whereas the creatinine-based chronic kidney disease epidemiology (CKD-EPI) formula can be used in geriatrics, obese patients, and patients already known to have decreased kidney function. The cystatin C-based CKD-EPI formula is for patients with HIV and post-transplant patients. Conclusion: This study identified that physiological conditions, especially patients' age and pathology, should be considered in devising formulae to estimate kidney function to accurately calculate safe drug doses.

Introduction
The assessment of patients' kidney function can be conducted through the estimation of the glomerular filtration rate (GFR). This parameter describes the number of functional nephrons and the amount of blood filtered per minute by the kidneys. It is known that GFR values can be used as an indicator to assess kidney function in determining the stages of kidney failure in patients since the lower the GFR value, the fewer the well-functioning nephrons (Inker et al., 2012; Maioli et al., 2020).

The estimation of GFR can be achieved by employing a mathematical formula incorporating creatinine clearance measurements. This approach is considered straightforward and feasible, as creatinine clearance can be determined by a 24-hour urine collection. Some formulae frequently used in practice are the Cockcroft-Gault (CG), Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology (CKD-EPI) equations (Casal et al., 2019). In selecting an estimation formula for kidney function, some patient factors (age, sex, and body weight) and drug factors should be considered to ensure the formula can describe the actual kidney function in drug secretion. This allows for selecting safe drug dosage, particularly for agents characterised by a limited therapeutic index.

Most drugs will be excreted to some extent in an intact form through the kidneys, making it necessary to adjust drug doses for patients with impaired renal function to prevent accumulation of drugs in the blood as well as toxicity. Numerous literature reviews and clinical trials have thus far examined the choice of formulae for estimating kidney function in patients. However, these studies have primarily focused on comparing the three most frequently employed formulae, CKD-EPI, MDRD, and CG, without considering the patient’s clinical conditions. Therefore, this literature review compares...
different formulae by considering patient age and clinical conditions, thereby allowing this to be an alternative guide to selecting a formula for assessing patients’ kidney function for both diagnostic purposes and the calculation of safe drug doses.

Methods
Search method
This literature review explored research articles published during the 2012 – 2021 period from the electronic media PubMed and ScienceDirect. The keywords used were (“assessment”) AND (“GFR”) AND (“formula”) OR (“renal function”) AND (“human”) AND (“Creatinine”). The selected articles fulfilled the inclusion criteria: articles published in English, focusing on formulae for kidney function assessment, and being available in full text. Articles were excluded if they were in the form of reviews and did not discuss formulae for kidney function assessment. The articles’ quality was assessed using the CONSORT item reference for articles about randomised controlled trials and the STROBE for articles focusing on observational-analytic investigations.

Results
The search found 46 articles, of which the quality was then evaluated. This resulted in 39 articles to review and 7 others to exclude because they did not meet the requirements. The scheme of the literature search in this review is shown in Figure 1.

Discussion
Assessment of kidney function in general
Kidney function estimation can be achieved by calculating the GFR, which relies on endogenous filtration indicators, such as serum creatinine. The creatinine concentration can be influenced by the synthesis of creatinine, which is contingent upon factors such as muscle mass and dietary intake. Consequently, estimating GFR that relies on serum creatinine levels can result in an overdiagnosis of chronic kidney disease (CKD). Based on these limitations, serum creatinine should ideally be part of the GFR, which requires correction modifications, such as age, weight, sex, and other factors.

The importance of GFR based on population studies using national population data concluded that the risk of decreasing GFR to mortality was influenced by patients' specific conditions such as age, comorbidities with DM, or hypertension (Kim et al., 2021). Yet, a systematic review of research articles published over a span of 20 years concluded that the difference in GFR values of 5 ml/min in 12-month eGFR was consistently shown to be associated with 20% increased risk of kidney transplant failure that ended in death (Mayne et al., 2021). In other words, a decrease of 5–10 mL/min
will be clinically significant if it occurs in patients with certain risk factors, such as advanced age or having previously experienced renal impairment.

Other parameters can also be used if endogenous filtration markers fail, including other endogenous and exogenous ones, such as cystatin C and iohexol. Cystatin C is a low-molecular-weight protein that is constantly synthesised by all cells within the body and subsequently excreted via the process of glomerular filtration (Wardhani et al., 2020). Meanwhile, is a non-radioactive exogenous chemical with a range of advantageous attributes. In general, the creatinine-cystatin C equation demonstrates a superior estimation of GFR compared to the individual use of creatinine or cystatin C. The reason for this is that cystatin C is less susceptible to the influence of muscle mass or food consumption, hence allowing for a more precise assessment of renal function (Björk et al., 2021). However, many applications for GFR calculation in Indonesia still use the CG, MDRD, and CKD-EPI formulae to date since they are more practical and affordable.

Principally, examination of kidney function is needed in certain conditions related to establishing a diagnosis or adjusting drug choices and doses. A GFR examination is not automatically performed when the patient, based on the doctor’s history, does not show symptoms or signs that require confirmation of the GFR value. In general, kidney function screening that can be done at a relatively cheap and practical cost is by proteinuria examination (Gowda et al., 2010). A national database involving nearly 150,000 subjects found that alongside systolic blood pressure values, proteinuria correlated significantly with GFR values (Hirayama et al., 2015).

It is widely acknowledged that most clinical pharmacokinetic studies use the CG formula for calculating kidney function scores to estimate drug doses, especially for drugs with a narrow therapeutic index. However, this formula is less sensitive when assessing the risk of kidney damage. This is consistent with a study (Ferreira et al., 2016) in which the CG formula does more regrouping for patients into higher stages of kidney damage, and results in GFR estimates that tend to be low among the elderly population. This is because calculating the CG formula involves the “140-age” variable. Consequently, elderly patients may exhibit a lower GFR despite having similar weight and creatinine levels. In contrast, the utilisation of the CKD-EPI formula is deemed to be more precise in classifying patients’ clinical risk compared to the MDRD formula. This is consistent with a study (Matsushita et al., 2012) which found that GFR estimates using the CKD-EPI formula exhibit superior performance in accurately categorising individuals at risk of death, acute myocardial infarction, and kidney disease as opposed to the MDRD formula.

**Estimation of kidney function based on age category**

**Children and adults**

The GFR may rise with advancing age due to proportional expansion in both the kidneys and the body. The height is the best parameter to replace the muscle mass in kidney volume assessment because creatinine is a by-product of muscle mass, whose value can change with the child’s growth. The Schwartz formula is considered one of the suitable equations for calculating GFR in paediatric and adult populations based on serum creatinine levels. This observation aligns with previous research, which found that the Schwartz formula is more suitable for individuals in the age range of 2-17 years, encompassing children and adolescents, as well as adults aged 18-40 years, who possess an estimated GFR value below 60 mL/minute/1.73 m² (Gao et al., 2013; Selistre et al., 2016). This formula exhibits favourable precision and accuracy, reducing bias compared to the CKD-EPI formula. The Schwartz equation is easy to use, especially in developing countries, since it does not require a computerised system or additional laboratory costs.

**The elderly**

The kidneys cannot regenerate, decreasing their function by up to 50% among the elderly aged ≥ 65 years. The aged population exhibits a decline in GFR, which can be attributed to diminished physical activity levels and reduced creatinine generation resulting from muscle mass depletion. The CKD-EPI formula employs age to ascertain the decline in muscle mass that often occurs with advancing age. Consequently, this leads to higher GFR values in adults compared to the elderly. Including age as a parameter in the CKD-EPI Formula leads to an upward bias in estimated GFR values for children and adults. However, in individuals aged 65 years or older, with an estimated GFR value of 90 mL/minute/1.73 m² or higher, the CKD-EPI Formula outperforms the Schwartz equation (Gao et al., 2013).

A study conducted by Inker et al. (2012) employed the CKD-EPI formula in conjunction with the creatinine-cystatin C combination to estimate the GFR within the range of ≤ 60-90mL/minute/1.73m². This study demonstrated that this approach yielded the most precise and accurate estimation of GFR values. Consequently, it can be considered a reliable confirmation test for diagnosing CKD. Furthermore, an investigation on individuals undergoing a consistent 12-month exercise regimen revealed that the CKD-EPI-
cystatin C formula outperforms the CKD-EPI-creatinine formula due to its reduced bias and smaller GFR values (Beetham et al., 2018).

Kidney function estimation based on pathological conditions

Obesity

Obesity is frequently defined based on the body mass index (BMI). Elevated BMI frequently correlates with the onset of renal pathology and perhaps a decline in GFR (Kim et al., 2021). In obese patients, BMI strongly correlates with the body surface area (BSA), making it necessary to normalise BSA to the standard (1.73 m²). If the GFR values are adjusted to the standard BSA, the resulting estimations of GFR tend to be lower, particularly when utilising a method that relies on creatinine-based calculations. However, if GFR is indexed to the actual BSA, it can increase by up to 50%. In weight loss programs for patients with extreme obesity, a cystatin C-based formula adjusted to the actual BSA can offer a more precise evaluation of renal function (Rothenberg et al., 2020). The utilisation of the CKD-EPI formula for estimating GFR in obese patients with chronic renal failure (CRF) is more effective when the CKD-EPI formula is used since it produces better precision and accuracy as well as a lower bias compared to the MDRD formula. This is useful when taking into account the drug doses and drug administration intervals (Januškevičiūtė et al., 2021). Furthermore, in patient care and clinical practice cases, administering the drug to patients with stable kidney function and extreme obesity CKD-EPI is an alternative to Cockcroft-Gault (Erstad & Nix, 2021). It should be noted that the consistent use of the same formula by healthcare providers is crucial for more accurate treatment recommendations. The validity of the CKD-EPI formula has been established in individuals who are obese, with a BMI ranging from 35 to 40 kg/m² and a GFR of approximately 60 mL/min/1.73 m² (Lemoine et al., 2014).

Decreased kidney function

A decline in renal function constitutes a risk factor for heightened morbidity and mortality. As the disease progresses, GFR will decrease rapidly, and there is a high risk of causing dangerous cardiovascular events. Therefore, as a risk marker, GFR should be calculated by using an appropriate formula to support better patient grouping and risk management (Weis et al., 2013). A study comparing the CKD-EPI formula and the Berlin initiative study-1 (BIS1) equation in the context of elderly patients with reduced kidney function showed that the BIS1 formula results in lower estimates of GFR and improves the reclassification of chronic kidney disease (CKD) prevalence (Polkinghorne et al., 2019). The CKD-EPI formula shows GFR estimates with good precision and accuracy, thereby improving the reclassification of CRF stages to a lower level (Browne et al., 2012; Rocco et al., 2016).

The measurement of GFR in elderly patients by iohexol plasma clearance has a bias contingent upon sample collection timing. A study (Ebert et al., 2015) A 24-hour sampling time can improve precision and accuracy and provide a more comprehensive evaluation of kidney function than a shorter sampling duration. Using the time point of blood sampling after 3 hours is recommended in paediatric patients since it produces a lower bias and acceptable precision for patients with stages 1-3 of CRF. However, for CRF stages 4-5, it is suggested that two-time points of sampling with a time range of up to five hours are used (Tøndel et al., 2018).

Meanwhile, an appropriate selection of the kidney function assessment formula for HIV patients is extremely important. Most antiretroviral drugs are eliminated and require dose adjustments based on kidney function. Previous research demonstrated a strong association between the CKD-EPI and MDRD formulas (Cristelli et al., 2017). Both of the formulas can be used to reclassify the stages of CRF. Additionally, the GFR determined by the utilisation of the CKD-EPI-creatinine method exhibits a diminished score and a tendency towards bias when compared to the CKD-EPI creatinine-cystatin C method (Zhao et al., 2021).

Post-transplantation

Kidney transplantation can help improve the overall well-being of those suffering from renal failure. Estimating early kidney function immediately after transplantation is crucial for making decisions on treating patients with post-transplant CRF to reduce the incidence of subsequent transplant or renal graft failure (Alhelal et al., 2020; Pieters et al., 2020). The comparison of the CG, MDRD, and CKD-EPI formulae in patients with post-transplant CRF, the findings revealed significant discrepancies in GFR values between the CG and MDRD formulae compared to the CKD-EPI formula. This result suggests that the incidence of individuals experiencing post-transplant CKD is significantly impacted by the selection of the formula used to estimate the GFR (Chroba et al., 2014). Another study revealed that the CKD-EPI-creatinine-cystatin C formula is better for post-transplant patients due to its high precision and accuracy in reflecting GFR changes over time (Kukla et al., 2014). The characteristics of the studies of the formulae for estimating kidney function based on patients’ pathological conditions are presented in Table I.
Table I: Characteristics of the research on estimation formulae for patients’ kidney function based on the pathological conditions

<table>
<thead>
<tr>
<th>Source and year</th>
<th>Study site</th>
<th>Study design</th>
<th>Aim</th>
<th>Method</th>
<th>Context</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Lemoine et al., 2014)</td>
<td>France</td>
<td>Retrospective study</td>
<td>To estimate the kidney function of obese patients in the process of CKD classification by GFR indexation</td>
<td>BSA-indexed or BSA non-indexed CKD-EPI formula</td>
<td>Obese patients with CKD stages 1-5</td>
</tr>
<tr>
<td>(Motie et al., 2017)</td>
<td>The United States</td>
<td>Randomised Controlled Trial (RCT)</td>
<td>To assess the short-term effects of intentional weight loss on the kidney function of obese patients</td>
<td>MDRD formula and modified CG formula</td>
<td>Obese patients</td>
</tr>
<tr>
<td>(Rothberg et al., 2020)</td>
<td>The United States</td>
<td>Prospective study</td>
<td>To assess and describe the impact of obesity and weight loss indexed to the standard BSA and actual BSA</td>
<td>CKD-EPI-creatinine, CKD-EPI-cystatin C, CKD-EPI-cystatin C, and MDRD formulae</td>
<td>Patients of the United States weight management</td>
</tr>
<tr>
<td>(Januškevičiūtė et al., 2021)</td>
<td>Lithuania</td>
<td>Retrospective study</td>
<td>To determine whether the modified formula can be a more accurate predictor of acute kidney injury (AKI)</td>
<td>CG formula modified with fat-free mass</td>
<td>Cardiac surgery patients</td>
</tr>
<tr>
<td>(Ebert et al., 2015)</td>
<td>Germany</td>
<td>Prospective study</td>
<td>To compare the measurements using iohexol clearance for 5 hours and 24 hours</td>
<td>MDRD, CKD-EPI, BIS1, and CG formulae</td>
<td>Elderly patients with a diagnosis of CKD</td>
</tr>
<tr>
<td>(Zhao et al., 2021)</td>
<td>China</td>
<td>Prospective study</td>
<td>To evaluate the kidney function and compare three CKD-EPI equations in a Chinese population</td>
<td>CKD-EPI-Creatinine, Cystatin C, and Cystatin-C-Creatinine formulae</td>
<td>Chinese patients with HIV/AIDS</td>
</tr>
<tr>
<td>(Sato et al., 2012)</td>
<td>Japan</td>
<td>Prospective study, RCT</td>
<td>To evaluate the Ishibashi formula, to compare the predicted AUC with the observed AUC</td>
<td>Ishibashi Formula</td>
<td>Chemotherapy patients of Tottori Hospital in Japan</td>
</tr>
<tr>
<td>(Takeuchi et al., 2021)</td>
<td>Japan</td>
<td>Prospective study, RCT</td>
<td>To evaluate and refine the formula</td>
<td>BSA-based trapezoidal formula</td>
<td>Cancer patients in Japan</td>
</tr>
<tr>
<td>(Beetham et al., 2018)</td>
<td>Australia</td>
<td>Randomised Controlled Trial (RCT)</td>
<td>To assess the GFR estimates based on cystatin C and creatinine after aerobic exercise</td>
<td>MDRD-creatinine, CKD-EPI-creatinine, CKD-EPI-cystatin C, and CKD-EPI-cystatin-C-creatinine formulae</td>
<td>Patients with CKD</td>
</tr>
<tr>
<td>(Chrobak et al., 2014)</td>
<td>Poland</td>
<td>Prospective study</td>
<td>To analyse the effects of selecting a post-transplant formula one year after surgery</td>
<td>CG, CKD-EPI, and MDRD formulae</td>
<td>Post-transplant patients</td>
</tr>
<tr>
<td>(Kukla et al., 2014)</td>
<td>The United States</td>
<td>Retrospective study</td>
<td>To evaluate the performance of two formulae in kidney transplant recipients</td>
<td>MDRD and CKD-EPI-creatinine or CKD-EPI-cystatin C-creatinine formulae</td>
<td>Post-kidney transplant patients</td>
</tr>
</tbody>
</table>

Note: CG = Cockcroft-Gault; MDRD = Modification of Diet in Renal Disease; CKD-EPI = Chronic Kidney Disease Epidemiology; BSA = Body Surface Area; GFR = Glomerular Filtration Rate; CKD = chronic kidney disease; AUC = Area Under the Curve

Conclusion

Estimating kidney function based on age can use the creatinine-based Schwartz formula. Meanwhile, for elderly patients aged >65 years, the creatinine-based CKD-EPI formula can be used. In addition, the elderly who take a regular exercise program are recommended to be administered the cystatin C-based CKD-EPI formula. The CKD-EPI-creatinine formula can be employed to estimate kidney function in patients with obesity and reduced renal function. For HIV patients, it is advisable to employ the CKD-EPI-cystatin C formula. The CKD-EPI creatinine-cystatin C formula differs from the aforementioned formula and is more suitable for post-transplant individuals. This review recommends further studies on the formula for estimating patients’ kidney function based on other physiological approaches, such as sexes, pregnant women, and lactating women who physiologically experience changes that can affect kidney function in excreting drugs.

Acknowledgement

The authors would like to thank Dr. Apt. Farida Hayati for providing valuable feedback on the manuscript and apt. Gita Mayasari, M.Sc, the clinical pharmacist of Yogyakarta City Hospital, for the in-depth perspective based on the conditions in a clinical setting.
References


Pharmacy Education 24(3) 322 - 328
Formulae for estimation of kidney function to calculate drug doses


