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REVIEW

Estimating glomerular filtration rate in kidney transplantation: Still searching for the best marker

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Abstract

Kidney transplantation is the treatment of choice for end-stage renal disease. The evaluation of graft function is mandatory in the management of renal transplant recipients. Glomerular filtration rate (GFR), is generally considered the best index of graft function and also a predictor of graft and patient survival. However GFR measurement using inulin clearance, the gold standard for its measurement and exogenous markers such as radiolabeled isotopes (^{51}Cr EDTA, ^{99m}Tc DTPA or ^{125}I Iothalamate) and non-radioactive contrast agents (Iothalamate or Iohexol), is laborious as well as expensive, being rarely used in clinical practice. Therefore, endogenous markers, such as serum creatinine or cystatin C, are used to estimate kidney function, and equations using these markers adjusted to other variables, mainly demographic, are an attempt to improve accuracy in estimation of GFR (eGFR). Nevertheless, there is some concern about the inability of the available eGFR equations to accurately identify changes in GFR, in kidney transplant recipients. This article will review and discuss the performance and limitations of these endogenous markers and their equations as estimators of GFR in the kidney transplant recipients, and their ability in predicting significant clinical outcomes.

Key words: Glomerular filtration rate estimation; Creatinine; Cystatin C; Kidney transplantation; Clinical outcomes

Core tip: An accurate evaluation of allograft function is essential in the management of kidney transplant. Glomerular filtration rate (GFR), is generally considered the best index of graft function. Endogenous markers, such as serum creatinine or cystatin C, are used to estimate kidney function, and equations using these markers adjusted to other variables, are an attempt to improve accuracy in estimation of GFR. This article will review and discuss the performance and limitations of these endogenous markers and their equations as estimators of GFR in the kidney transplant recipients, and their ability in predicting clinical outcomes.

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INTRODUCTION

Kidney transplantation is the treatment of choice for end-stage renal disease. A successful kidney transplant improves the quality of life, reduces the mortality risk for most patients and is less costly when compared with maintenance dialysis[1-3]. The significant progress that has occurred over the last two decades in renal transplantation is mostly driven by improvements in short-term graft survival whereas long-term outcomes remained largely unchanged[4,5]. Nowadays, with the traditional short-term outcomes, namely the 1-year graft and patient survival rates in excess of 90% and 1-year acute rejection rate of less than 15%, the question arises if any further improvements are possible or even necessary[6]. However, these outstanding results have failed to anticipate long-term survival, so it becomes clear that identification of new, short-term end points capable of correlating with long-term graft outcome is necessary[7] ideally translating in longer graft maintenance.

Renal allograft function seems to be a tempting candidate as surrogate marker for research studies on transplantation[8], also for the assessment of new drugs[9,10], although its use as an outcome marker for graft loss is controversial[11,12]. In generally, the glomerular filtration rate (GFR), is considered to be the best index of overall kidney function[13,14], also an indicator of long-term graft survival[15], and an independent risk factor for cardiovascular mortality[16,17], the primary cause of death in kidney transplant recipients[17,18]. Of note, like in non-transplant chronic kidney disease, prevalence of complications related to loss of renal function such as hypertension, anemia and abnormal mineral metabolism increases significantly as the GFR declines[19]. Another important point is that the decline in GFR is also related with increased health care costs, and over the two years, transplantation was both more effective and less costly than dialysis[2,3]. Therefore, an accurate evaluation of renal allograft function is crucial in the clinical management of kidney transplant recipients.

Methods to measure GFR using exogenous markers, such as inulin clearance, the gold standard, and others such as radiolabeled isotopes (^{51}Cr EDTA, ^{99m}Tc DTPA or ^{125}I Iothalamate) and non-radioactive contrast agents (Iothalamate or Iohexol), are laborious as well as expensive, being rarely used in clinical practice. Therefore, endogenous markers, such as serum creatinine (SCr) or cystatin C (CyC), are used to estimate kidney function. Mathematical formulas employing these markers adjusted to other variables (mainly demographic) are an effort to ameliorate GFR estimation (eGFR) accuracy.

However, there is some concern about the accuracy of the available eGFR equations in kidney transplant recipients and guidelines still provide conflicting recommendations about GFR estimation methods in this population[20].

In this article, we aim to review the performance and limitations of these endogenous markers and their equations as estimators of GFR in the kidney transplant recipients, and their ability in predicting significant clinical outcomes.

ENDOGENOUS MARKERS

SCr

SCr concentration is the best known and most commonly used marker for estimation of GFR, since it was first described as a GFR marker in 1937[21], and SCr analysis is inexpensive and generally accessible. Creatinine is a breakdown product of creatinephosphate in muscle tissue, produced at a relatively constant rate, depending on the muscle mass, and filtered in the glomerulus but also actively secreted in the proximal tubule[22]. Tubular secretion contributes normally to 10% of renal Cr removal, but increases when GFR decreases[23], causing SCr to remain in the normal range until GFR drops below 60-70 mL/min. Some Cr is also incorporated from the diet. Ingestion of meat contributes substantially to the urinary Cr excretion, both as a result of expansion of the total creatine pool and as a result of gastrointestinal absorption of Cr[22]. Thus, multiple factors contribute to reduce the accuracy of SCr as an indicator of the GFR, including sex, age, race, muscle mass and dietary protein intake.

Particularly, in renal transplantation there are other determinants that may interfere with Cr metabolism such as corticosteroids, which have a direct catabolic effect[24] and cause a changed muscle mass ratio to total body weight[25]. Catabolic illnesses such as infection and acute rejection, and prolonged dialysis, can also be partly responsible[26].

Cr tubular secretion can be blocked by some drugs such as trimethoprim, commonly used in kidney transplantation[27]. Also, chronic rejection and acute tubular necrosis, can contribute, because tubular secretion of creatinine is reduced.

Because Cr secretion is not predictable, the GFR can decrease to nearly half the normal value before the SCr increases[13], with remarkable consequences in kidney transplant outcome, where subclinical progressive damage, such as calcineurin toxicity and rejection will not be early identified. Several studies in kidney transplantation demonstrated that the SCr and GFR were barely correlated[26,28].

In addition, SCr measurement by the most common method (Jaffé) is subject to interferences by chromogens such as bilirubin, glucose and uric acid, and the enzymatic method is prone to interference by bilirubin and some antibiotics. Considerable variations between SCr assays calibration may also cause inaccuracies in its determination[29]. An attempt to standardize measurement

has been recently introduced by adoption of a common calibration to isotope dilution mass spectrophotometry standard (IDMS) with substantial improvement and traceability of SCr measurements[30].

Nonetheless, SCr is recommended as a screening test for changes in allograft function[31], adjustments of immunosuppressive drugs[32], and it was shown that SCr by itself may be a predictor of long-term graft and patient survival[33].

Creatinine clearance

Creatinine clearance (CCr) as measured from 24-h urine collection is often used in clinical practice to calculate GFR, but it overestimates GFR due to the secretion of Cr by the renal tubules and the inherent limitations of SCr as a kidney marker. However, this calculation does not correct for tubular secretion, and overestimates GFR also in transplant populations[28,34,35], with additional errors in urine collection. Measurement of CCr using this method becomes more reliable after the administration of cimetidine, which inhibits tubular secretion[36], but still does not supply additional knowledge about renal function than other Cr-based methods[13,14].

Serum CyC

CyC is a 122-amino acid, 13-kDa protein that is a member of a family of competitive inhibitors of lysosomal cysteine proteinases. Its functions include involvement in extracellular proteolysis, immune modulation, and antibacterial and antiviral activities.

CyC has certain characteristics that make it an acceptable candidate as a kidney function marker, including a constant production rate, free glomerular filtration, complete reabsorption and catabolism by the proximal tubules with no reabsorption, and no tubular secretion[37].

Several clinical data demonstrated that serum CyC levels correlate better with GFR than does Cr alone, especially at higher levels of GFR, and it was also thought to be less influenced by certain demographic factors such as age, race, gender, or muscle mass compared with SCr[38,39]. However, some emerging new data have shown that serum CyC may be influence by these and other variables.

A recent study concluded that CyC was 9% lower in women and 6% higher in blacks for a given GFR[40]. In a cross-sectional study, Knight *et al*[41], found that older age, male gender, greater weight, greater height, current cigarette smoking, and higher serum C-reactive protein levels were independently associated with higher serum CyC levels after adjusting for CCr.

Moreover, in certain clinical settings, CyC level may be biased as a marker of kidney function, such as in patients with uncontrolled thyroid disease, rapid cell turnover, and those under steroid therapy[42], like kidney transplant recipients. Also, CyC is quite costly and unavailable in many transplant centers.

GFR ESTIMATION FROM SCR BASED EQUATIONS

To overcome some of the limitations of Cr as a marker for GFR, several formulas have been constructed to correct for the influences of weight, age, gender and/or race[26,43-46].

Some of these equations have been evaluated in renal transplant patients, and the most commonly used are the Modification of Diet in Renal Disease (MDRD) study[44], Cockcroft-Gault[43], and Nankivell[26] equations. The KDIGO position statement includes the proposal that Cr-based eGFR equations should be used to evaluate renal function in the everyday management of renal transplant recipients[14].

The Cockcroft-Gault equation was derived in 236 (96% male) hospitalized patients with a wide range of GFR values[43]. The MDRD equation, published in 1999 were derived in 1628 patients with chronic kidney disease (mean GFR, 40 mL/min per 1.73 m^2)[44], and this was simplified in 2000[47] and reexpressed in 2005, after standardization of the SCr assays to the reference method using IDMS[48,49]. The Nankivell equation is the only one that was derived from kidney transplant recipients[26], however some of these transplant patients were in an early post-transplant phase or with acute dysfunction, which has implications in prediction of GFR.

More recently, a new formula was published by the chronic kidney disease epidemiology collaboration (CKD-EPI)[50], to overcome the systematic underestimation of GFR and lack of precision of the MDRD formulas in patients with relatively well-preserved kidney function, but only 4% of the CKD-EPI derivation cohort consisted of organ transplant recipients.

PERFORMANCE OF CREATININE-BASED GFR ESTIMATION EQUATIONS IN KIDNEY TRANSPLANTATION

To certify graft function as a valid surrogate marker, we must know for certain that we use a solid measure of kidney function.

The eGFR equations were an alternative to estimate GFR in clinical context, as they allow us to overpass some of the limitations of the SCr[51].

To determine the performance of a given eGFR equation the K/DOQI guidelines[13] proposed a methodological approach according to simple and reproducible criteria: "BIAS", "PRECISION" and "ACCURACY". The absolute BIAS expresses the systematic deviation from the gold standard measurement of GFR, and was given by the mean difference between estimated GFR and gold standard clearance (true GFR). The relative BIAS, hereafter named percent BIAS, is expressed as the proportion of true GFR represented by the absolute bias, and was calculated as: absolute BIAS/true GFR × 100. PRECISION expresses the

variability or dispersion of predictions around the true GFR and corresponds to the standard deviation of the difference between the true and estimated GFR. The distribution of the differences between estimated and true GFR accounts for the ACCURACY of the GFR estimates (*e.g.*, 30% accuracy is the proportion of predicted GFR within ± 30% of the true GFR).

In several studies in kidney transplantation, the efficiency of MDRD, Cockcroft-Gault and Nankivell equations has been consistently reviewed[52], with a significant heterogeneity between studies, with low precision inducing limited accuracies, and this can be attributed to varied patient characteristics, differences in measure GFR methods and Cr assay calibration and, potentially, some inherent differences in this specific population of transplant recipients[52]. In the majority of these studies, all of these equations persistently testified progressive decrease in GFR overestimation and/or increase in GFR underestimation as graft function ameliorated [28,34,53].

The CKD-EPI equation[50] introduces a correction term to overcome the systematic underestimation of GFR of the MDRD formulas in patients with relatively well-preserved kidney function, as mentioned above. In a cohort of 207 stable Kidney transplant recipients[54] CKD-EPI shows improved estimation ability compared with MDRD equation, but still with suboptimal precision that limit the value of the CKD-EPI for monitoring changes in kidney function over time[54]. Other studies compare the performances of the MDRD and CKD-EPI equations in a large transplant patient's cohort[55,56] and the authors concluded that the latter equation does not offer a better GFR estimation in this population.

More recently, Shaffi *et al*[57], conducted a systematic evaluation of the development methods of all published Cr-based eGFR equations, and assess their performance in a large population (n = 3622) of solid-organ transplant recipients, including 53% kidney transplant recipients. They founded that the CKD-EPI[50] and IDMS-traceable 4-variable MDRD Study equations[48] were more accurate than the alternative equations, including those developed in populations including only transplant recipients, and as accurate as observed in non-transplanted populations. Nevertheless, we can't forget that these equations still misestimate true GFR by > 30% in 1 of 5 patients.

They also concluded that there was no difference between these two equations in the overall study population, but CKD-EPI equation showed better performance at higher GFRs compared with better performance of MDRD Study equation at lower GFRs, which is in agreement with the results of the systematic review performed by Earley *et al*[58]. This study[57] may have implications in clinical practice, support the use of these eGFR equations to routine access renal function in transplant patients as in other populations. Even though it was a good diagnostic test study design with a standardized reference test, the study population included few nonwhites and individuals with solid organ transplants other than liver and kidneys; therefore assessment of the equation performance in these subgroups is limited[57].

However we can't ignore that SCr levels are affected by factors besides GFR, and several studies suggest worse stage-based care in kidney transplant patients compared with native kidney diseases[59,60], so any eGFR equations based on SCr still have limitations.

PERFORMANCE OF CYSTATIN-BASED GFR ESTIMATION EQUATIONS IN KIDNEY TRANSPLANTATION

As with SCr, it is the CyC-based GFR, rather than the CyC itself, that is of greater clinical interest. Over the last decade, several serum CyC-based equations have been developed and proposed to estimate the GFR[61-67].

Only two of these equations (Rule *et al*[64] and Le Bricon *et al*[67]) were exclusively derived from a population of kidney transplant recipients.

Several studies in the renal transplant population, showed discordant results with some indicate advantage of CyC-based equations over Cr-based equations, whereas others showed no superiority of CyC over SCr[20,34,68]. One of the limitations of CyC-based eGFR formulas in this population is that the treatment with corticosteroids increases CyC levels by increasing the production of CyC[69]. Although the KDIGO recommendations on kidney transplantation comment the possible interest of using CyC to GFR estimation, they do not advocated its regular clinical use, due to the paucity of validation studies in this group of patients[20].

A recent systematic review[70], identified 10 studies, evaluating the accuracy of 14 different CyC-based eGFR equations in renal transplant recipients. The authors conclude that the Le Bricon equation[67] was the highest accurate, and the majority of the CyC-based equations exhibited 30% and 50% accuracy improvements compared with the Cr-based MDRD equation. However, as with the Cr equations, there was substantial variability between the studies. Much of this variability is consequence of different study populations, differences in the GFR reference standard measurement, and in variation in the calibrators for the CyC measurement, and this latter contributes to the greatest source of variation. Standardized reference material for CyC has already been developed[71], but none of the studies involved in this analysis[70], adopted this methodology.

In 2008 a new Cr- and CyC-based formula (CKD-EPI CyC equation) was developed[40], which besides serum CyC includes the variables of gender, age and race, and seems more accurate than the formulas based on Cr or CyC alone, but this formula requires further testing in various patients groups.

Recently, the CyC-based estimating equations were re-expressed for use with the standardized CyC reference material (ERM-DA47/IFCC)[72]. These and the equations with CyC in combination with SCr[40], improved in 2012 with lesser bias at GFR > 60 mL/min

(CKD-EPI Cr-CyC 2012)[73], were validate in a European cohort of renal transplants patients[74] but their accuracy needs to be evaluated in more studies with this population.

CREATININE-BASED AND CYC-BASED eGFR EQUATIONS AS PREDICTORS OF CLINICAL OUTCOMES

Although, it has been demonstrated that eGFR is a predictor of patient and transplant survival[75], disappointing results have been reported when several of Cr-based eGFR formulas where assessed against the most important outcome measures such as mortality and graft failure, with limited utility and no benefit over the use of SCr alone[76].

Another relevant problem in clinical practice is whether the eGFR equations were able to precisely predict variations in graft function over time. Several studies reported considerable variability of the Cr-based eGFR equations performance at different times post-transplant[28,77] with less accuracy within the first year of transplantation[78], indicating that those Cr-based equations must be worn with caution for GFR monitoring through time[79].

Nowadays there is an increasing interest in CyC-based equations as an outcome predictor in kidney transplantation. In general population, CyC-based eGFR equations are a stronger predictor of the risk of death and cardiovascular events, when compared with Cr[80,81], as well as the correlation of serum CyC with all-cause and cardiovascular mortality in chronic kidney disease (CKD)[82]. Recently, a meta-analysis of 11 general-population studies and 5 studies of cohorts with CKD[83], shows that the utilization of CyC alone or in combination with Cr reinforce the power of eGFR as a predictor of end-stage renal disease and death .

Whether this outcome prediction is true for transplant recipients needs to be confirmed. Although, some studies showed that CyC and or CyC-based equations predicted both patient mortality and graft outcome better than Cr-based eGFR equations[34,84], others founded that CyC and SCr were equally reliable predictors of graft outcome[85].

Interestingly, very recently, a study examined the extent to which the addition of serum CyC improves GFR estimation and mortality prediction, in comparison to various eGFR equations, in a population of 401 liver transplanted patients. In this work, the authors founded that CyC, by itself or as a part of an eGFR, was a significant predictor of mortality[86].

Another approach is a multimarker management, including combination of different markers of graft function, such as SCr, CyC, and kidney pathologic markers, such as proteinuria and/or albuminuria. Models that include Cr-based or CyC-based eGFR and albuminuria show better prediction to end-stage renal disease in general population[87,88], and CKD patients[89].

A clinical score constructed from a cross-validated French database of 2169 kidney transplant recipients, combining risk factors of graft loss, including SCr and proteinuria, demonstrated to be highly predictive of long-term kidney graft survival[90], and other study demonstrated that the combination of low-grade albuminuria and decreased eGFR was related with graft loss and mortality[91].

In a similar way, a recent small-sample single-center study[92] founded that predictors combining albuminuria and Cr- or CyC-based eGFR, performed better than those markers alone, to predict death censored graft loss, in kidney transplant recipients. Moreover, the best predictor of graft failure in this work was a product of CyC and the logarithm of albuminuria, and CyC-based predictors performed better than Cr-based predictors.

More recently, there has been some enthusiasm in new markers of kidney injury such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1), and it potential in prediction of kidney function, not influenced by age, gender, race, body fat and muscle mass. Particularly, in kidney transplant recipients, it was demonstrated that urinary excretion of KIM-1, a proximal tubular protein, independently predicts graft failure[93]. However, more trials are required to validate these results in clinical setting.

PROTEINURIA

Proteinuria, although not a direct GFR marker, is also an important indicator of allograft dysfunction[94,95], associated with a reduced long-term graft survival[94,95] and increased patient mortality[94,96].

One of the limitations of proteinuria as an accurate marker of graft dysfunction is the native kidney excretion, and in that cases, should have a baseline value before transplantation, particularly in the setting of pre-existing glomerular disease. However, pretransplant proteinuria decreases or disappears after successful transplantation and *de novo* or increasing proteinuria is indicative of graft pathology[97].

Proteinuria can signal pathologic changes including recurrent or *de novo* glomerular disease, calcineurin inhibitor toxicity, alloantibody-mediated injury and chronic allograft nephropathy[98]. In this way, graft biopsy helps to determine the etiology of proteinuria[20,99] and to manage some treatable causes of graft injury. KDIGO guidelines[20] proposed monitoring of proteinuria as part of routine transplant follow-up.

CONCLUSION

An accurate evaluation of allograft function is crucial in the management of kidney transplant, and most importantly in predicting clinical outcomes. However any endogenous kidney function marker has limitations, and understandably, eGFR formulas derived from them will present similar barriers. Also, these prediction equations have inherent problems, namely the selected

populations used for their derivation, usually non-transplanted patients.

The Cr-based eGFR equations were the much widely used and recent studies, accessing the performance of MDRD study and CKD-EPI equations in kidney transplantation, support their use to routine access renal function in transplant patients as in other populations. But, we can't forget that Cr-based eGFR equations have never been demonstrated to improve the clinical recognition of changes in transplant function, compared to the use of Cr alone, and many transplant injuries occur without change in SCr level or eGFR.

In the last years, our attention is moving toward another markers and CyC seems to be a promising one. Although, some conflicting results, several studies in kidney transplants confirm the better performance of CyC-based equations over Cr-based equations in estimating GFR. The use of CyC alone or in combination with Cr reinforces the eGFR power as a predictor of end-stage kidney disease and death, in general and CKD population, but we need to confirm this outcome prediction in transplant recipients. However, like Cr, CyC is also influenced by non-GFR determinants, is more expensive than SCr and has suboptimal standardization, therefore its use is not widespread implemented.

Finally, a model combining different markers such as SCr, CyC, proteinuria and/or albuminuria can be useful in clinical practice, providing an improvement in outcome prediction. At moment, and regarding the kidney transplant management, we are still searching for the optimal combination and for the best marker.

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