

Identifying Kidney Dysfunction after Renal Transplantation: The Role of Biomarkers and Different eGFR Formulae

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Received May 21, 2019; Revised May 28, 2019; Accepted May 30, 2019

ABSTRACT

Graft dysfunction can result from ischemic damage or immunological injury that lead to serious consequences in both the short and the long term. There is a need for biomarkers of graft injury secondary to both immune and non-immune injuries at distinct time periods of the transplantation process. This is relevant in the initial phase of renal transplantation commencing from the potential kidney donor where the acute kidney damage can go unnoticed and also in the early post-transplant phase in the renal transplant recipient for predicting acute transplant dysfunction. Long-term assessment of kidney function is also relevant to detect graft dysfunction early. The use of novel biomarkers can be useful to identify early graft dysfunction. In addition, several methods of estimating glomerular filtration rate are in use, which can be useful in detecting changes in renal function during long-term monitoring post-transplantation. The purpose of this report is to review the role of these novel biomarkers and different methods of estimating glomerular filtration rate in the renal transplant recipient.

Keywords: Biomarkers, Renal transplant, Primary graft dysfunction, eGFR formulae

INTRODUCTION

Graft dysfunction after renal transplantation can be due to immunological and non-immunological injury. Both mechanisms can be associated with poor outcomes in both the short and long term. In the study by Bagshaw et al. [1], acute kidney injury was defined as an increase in the levels of creatinine of 15% or more above baseline. After transplantation, urine output can be actively monitored in the initial few days and any decline to the level of oliguria or anuria used to identify early graft dysfunction. An increase in the serum creatinine is a late sign of renal dysfunction and a sensitive marker to detect renal dysfunction early is needed. This is supported by Salvador et al. who pointed out that after transplantation of both renal and non-renal organs, a significant number of the patients develop renal dysfunction [2]. Conventional urinary biomarkers such as casts and fractional excretion of sodium are insensitive and non-specific for the early recognition of acute kidney damages.

Other tests characterized by increased levels of insensitivity include the high molecular weight proteins and tubular proteins which are filtered were equally ignored. The tests that were preferred were integrated with the new

technologies including the functional genomics and proteomics which were used in uncovering the novel candidates emerging as potentially applicable biomarkers in the cases of non-transplant acute kidney damage. Finally, it was noted that the best future practice would be using the plasma panel which is typically comprised of the Neutrophil Gelatinase-Associated Lipocalin (NGAL) which are developed in the non-transplant acute kidney injury. The aspects that were prioritised in the process included the existence of a prolonged cold ischemic time, donor history of hypertension, kidney donor profile index and preformed donor-specific antibodies.

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Citation: Al Mutawa KA, Halawa A & Camilleri B. (2019) Identifying Kidney Dysfunction after Renal Transplantation: The Role of Biomarkers and Different eGFR Formulae. *J Renal Transplant Sci*, 2(3): 121-127.

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BIOMARKERS THAT HELP IDENTIFY GRAFT DYSFUNCTION EARLY

A biomarker can be defined as a non-invasive tool in diagnosing renal transplant complications which are common in the clinical practice. These biomarkers are customarily used on top of the clinical and pathological markers. Biomarkers may play an instrumental role in diagnosis or identification of a particular disorder. With regards to renal dysfunction, they also have a role in staging of the severity or level of the renal impairment, disease prognosis and predicting and monitoring the clinical responses to the intervention. Salvadori et al. [3] has pointed out the increased progress in the field of genomics and proteomics which leads to the findings of robust, predictive and useful biomarkers.

These biomarkers include plasma panel which is typically comprised of the NGAL which are developed in the non-transplant acute kidney injury. Additionally, there are biomarkers that are focused on the T-cell activity and innate immunity which are all plasma associated. Others include CXCL9, CXCL10, C-C motif chemokine ligand 2 (CCL2), IL-18, cystatin C, kidney injury molecule-1 (KIM-1), T-cell immunoglobulin and mucine domains-containing protein 3 (TIM3) which are found in the urine [4].

Urinary TIMP-2

Tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin associated growth factor binding protein 7 (IGFBP7) represent one of the promising biomarkers in the acute kidney injury. This biomarker has attracted very recent research works and as such it is in its initial phases of use in the kidney transplantation. In a recent study by Maizel et al. [5], it has been noted that the TIMP-2 is released by the tubular cells exposed to the septic or the hemodynamic aggression. Its implication is on its capacity of predicting the development of AKI within a period of 12-24 h. Johnson and Zager [6] observed that the early diagnosis of AKI is critical in an event the therapeutic interventions leverage on the best opportunity for mitigating evolving renal damage. Despite BUN and plasma creatinine elevations are identified as the most broadly appreciated AKI biomarkers, an identifiable increase in the products could lead to delay for 24-72 h after the AKI induction. Hence, a reliance on the other biomarkers could lead to critical interventional delays. The consequence of this has been a multigenerational search for the AKI biomarkers permitting a prompt diagnosis of the early and/or subtle renal damage. This is the situation that has been identified from the studies carried out on different critical care patients and in different settings such as the emergency room, post-cardiac surgery and septic patients. The limitation of this biomarker is that it is not clear on whether the baseline urinary concentrations are equally linked with the risk of the progression from the mild and moderate to severe AKI. Also, Johnson and Zager [6] study pointed out on the issue of the low molecular mass of TIMP-2 hence

limiting the level of filtration of the protein. As such, a situation of the biomarker escaping a successful reabsorption by the damaged proximal tubules and as such makes a direct contribution to the elevated urinary levels. In this case Bank et al. [7] pointed out that the TIMP-2 effectiveness is used in predicting the presence and duration of delayed graft function in donation after circulatory death kidney transplant recipients. As such, this is used as a promising biomarker adopted in the prediction of the occurrence and duration of the biomarker in the kidney transplant recipients. This is since the delayed graft function is linked with the increased numbers of the kidney biopsies which is carried out at an early phase of post transplantation, a prolonged hospitalization and increased costs of transplantation.

Neutrophil gelatinase associated lipocalin (NGAL)

NGAL may be referred to as the most commonly used novel biomarkers within patients with graft dysfunction and acute kidney injury [8]. It was initially observed as a component associating with gelatinase of a disulfide-linked heterodimer secreted by neutrophils. However, NGAL may also be found in neutrophils but without the presence of gelatinase. The extent of the novel biomarker NGAL is usually observed at very limited levels and is usually present within various human tissues such as lungs, colon, stomach and kidneys. The NGAL is nevertheless used as a biomarker despite being a sensitive and specific early marker of distinct etiological classes of acute kidney injury for classification of the renal injury and dysfunction. An elevated NGAL levels has been noted to contribute to cases of heart failure, coronary heart disease and stroke [9]. The outcome of heart failure cases is best predicted by the renal marker as opposed to the cardiac markers. NGAL has equally been found to directly correlate with the cardiovascular events and mortality rates despite of it not being conclusive yet.

Kidney injury molecule-1 (KIM-1)

KIM-1 may be referred to as a transmembrane protein with mucin and immunoglobulin domains. The interpretation of KIM-1 in diagnosing renal injury induced at an early stage is usually based on proximal tubule component [10]. The relative transmembrane protein component of KIM-1 is usually present within kidneys of both humans and animal models. In the study by Zhang et al. [10], it can be noted that KIM-1 is normally excreted from proximal tubule cells and interpreted based on the perceived analysis of kidney biopsies. As demonstrated by Cruz et al. [9], KIM-1 is identified as a blood biomarker that specifically reflects acute kidney damage. The significance of this is that the KIM-1 is normally expressed in the tubular epithelial cells prior the blood biochemical indexes becoming elevated and morphological changes occurring. The advantage of this is that the KIM-1 expression is the most early, sensitive, and specific biomarker in determining the renal tubular epithelial cell injury in renal allograft tissue.

Interleukin 18 (IL-18)

IL-18 is usually known as a persuasive pro-inflammatory cytokine produced by macrophages and other cells being observed within the cases of reperfusion injuries as noted in Levey et al. [11]. The production of IL-18 is usually increased markedly within the cases of urinary tract infections which later on evolved in the form of exploration of chronic kidney diseases [12]. The process of acute kidney rejection may be successively and efficiently diagnosed on the basis of appropriate observatory analysis of IL-8 [11].

VALIDATION OF ESTIMATED GLOMERULAR FILTRATION RATE (eGFR) FORMULAE IN PATIENTS AFTER RENAL TRANSPLANTATION

The use of estimated glomerular filtration rate (eGFR) formulae in the patients after a successful renal transplantation will be reviewed next. This is informed by the view that eGFR that is calculated from serum creatinine using an isotope equation is a simple and effective approach where different laboratories can assist the healthcare providers in detecting any health issue among the risk factors in kidney disease. Also, the extent in which providers could adopt the use of eGFR in monitoring the patients already diagnosed with CKD. This section focuses on the Modification of Diet in Renal Disease (MDRD) equation approach and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) approach [12].

MDRD equation approach

The MDRD can be identified as a formula used in the estimation of the glomerular filtration rates (GFR). Hornum et al. [13] pointed out that an assessment of eGFR is critical in kidney transplantation as it is a transplant equation used to estimate the GFR as compared to other equations used for the GFR estimation in different patients. This is for instance evident from the chronic nephrotoxicity and high doses of calcineurin inhibitors which are critical factors. Also, the MDRD is less bias for the transplant patients as opposed to the other equations. This formula had been validated on patients who are suffering from chronic renal disease. Nevertheless, in the patients who have gone through successful renal transplantation, there have been instances where their overall performance has significantly deteriorated. From this, the researchers have recommended the need of integrating a GFR equation which has been lacking in the past. This could be influenced by issue of being in a position of performing a precise and a more valid measurements or estimates of renal function in the patients. This is for the sake of accurate and safe dosing of immunosuppressive medication and performing an adjustment of the treatment and prophylaxis of renal dysfunction.

The application of the MDRD eGFR usually is when the SCR is reported in $\mu\text{mol/L}$. This equation should not be used when eGFR values are above $60 \text{ mL/min/1.73 m}^2$ and it is

recommended when eGFR values are below $60 \text{ mL/min/1.73 m}^2$.

The MDRD equation is not valid in certain situations including individuals or patients who have extreme body types. This is also applicable to patients suffering from a limb amputation with severe malnourishment and morbidly obese people. MDRD formula is also not suitable for patient with normal or near normal renal function, as it tends to underestimate the renal function. In this phenomenon, the most appropriate approach is to ensure a constant testing, evaluation of the decline in renal function in a timely manner and measurement of cystatin C. The focus is also inclusive of other additional indicators of renal disease such as urinalysis.

In addition, eGFR values measured by MDRD equation often differ between different laboratories. In some instances, creatinine measurements vary significantly between different laboratories based on the approaches used in the measurement process. Many laboratories tend to adopt a diverse formula for calculating the eGFR. This is done in a more improved practice leading to complications of the comparisons of the eGFR measurements sourced from the different laboratories. This is often complexed by the fact that the approach is costly and imposes a critical burden; In addition, MDRD eGFR formula is valid when the calculations assume that the levels of the creatinine are stable over days or a more extended period. It is hence not valid for patients who are found suffering from acute kidney injury.

All these limitations have been identified in patients who have already gone through renal transplant. Therefore, to mitigate these limitations, it is recommended to use a traceable marker to the gold standard of creatinine determination which would successfully mitigate any problem with the renal transplanted patients.

CKD-EPI equation approach

The use of Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation approach evolved with the purpose to provide a more accurate estimate of glomerular filtration rate (GFR) in individuals with normal or mildly reduced renal function. The most prominent aspect in terms of using relative CKD-EPI equation approach refers to the fact that the practice of such approach also gives accurate estimations within those cases in which the patients has a higher rate of GFR [13]. The use of CKD-EPI equation evolved as a result of the ineffectiveness of MDRD equation within estimations of higher GFR. The use of CKD-EPI equation proves extremely feasible in obtaining accurate and exact estimations of the higher GFR and such approach is usually used within those cases in which the GFR exceeds 90 mL/min . The use of such equation also proves extremely useful in avoiding over-diagnosis of CKD cases. This equation started to evolve during the year 2009 and since

then has been considered as one of the most widely used methods to estimate GFR and analyze renal function in renal transplant recipients. The enhanced accuracy of the CKD-EPI equation in estimation of GFR is the main reason behind its acceptance across the world for such purposes [14,15].

How is EPI eGFR different from MDRD eGFR?

In adults, it can be noted that the most popular equations applicable to estimate GFR as sourced from the serum creatinine are the CKD-EPI equation and the Isotope Dilution Mass Spectrometry (IDMS) traceable Modification of Diet in Renal Disease (MDRD) Study equation. The application of the MDRD eGFR usually is when the S_{CR} is reported in $\mu\text{mol/L}$. This equation should *not* be used when eGFR values above $60 \text{ mL/min/1.73 m}^2$ which are essentially demanded. In case the measures do not fit the use of the MDRD eGFR, the CKD-EPI eGFR is applicable in

the tests. The CKD-EPI eGFR creatinine equation is founded on similar four variables as the ones found in the MDRD study equation. Nevertheless, it tends to adopt a 2-slope for modelling the existing relationship between the estimated GFR and serum creatinine and a different relationship existing for the factors of age, sex and race. As noted by Pottele et al. [16] this equation is useful in that it performs an enhanced role and with limited bias as opposed to the MDRD studies equation. This is particularly the case for the patients who have been found to possess an increased level of GFR. The consequence of this is the misclassification of the CKD. The differences in this context are evident from the fact that from November 2009, some clinical laboratories reports have estimated the GFR through the use of the CKD-EPI eGFR creatinine equation. **Figure 1** demonstrates the estimated GFR in CKD-EPI and the MDRD study and the accuracies of the equation.

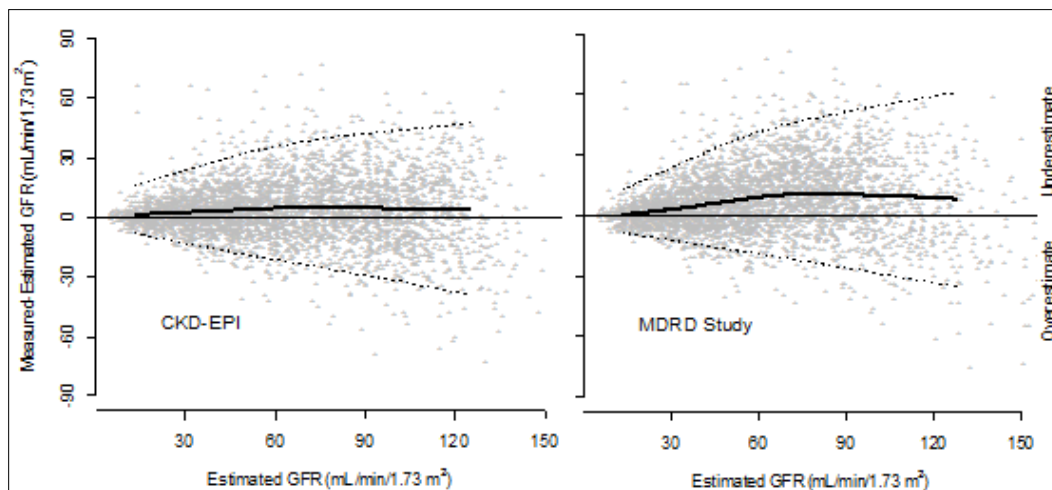


Figure 1. How EPI eGFR is different from MDRD eGFR?

Accuracy of the CKD-EPI and MDRD equations to estimate GFR for the validation data set (N=3896). In this figure, both panels show the difference between measured and estimated (y-axis) vs. estimated GFR (x-axis). A smoothed regression line is shown with the 95% CI for the distribution of results, using quantile regression, excluding the lowest and highest 2.5% of estimated GFR

Source: Pottele et al. [16]

Quality of studies validating CKD-EPI formula in patients after renal transplantation

Many studies demonstrated the extent to which accurate calculation of GFR is critical in the successful management of the patients after kidney transplantation. It has equally integrated the use of the CKD-EPI formula introduced for estimating the GFR in chronic kidney disease patients. Additionally, the use of the pooled data of a total of 8254 participants sourced from a total of 10 studies and an active validation of a total of 3896 participants who had been sourced from an additional 16 studies [11]. From this large sample, the study recommended that the MDRD formula had a positive implication in different patients but compromised of issues leading to an improved and an ideal estimation formula. Hence, the question of the study on deducing of

the new CKD-EPI equation has any influence on harnessing an increased MDRD equation and if it would present any positive advantages for the used GFR calculation among the targeted patients after the KTx. This is as noted by Kolsrud et al. [17] who noted that pre-transplantation $Mgfr$ is not in any way predictive of mortality but necessitated simultaneous or late-stage KTx in the selected population of patients.

Limitations of CKD-EPI formula in the estimation of GFR

The CKD-EPI equation is an establishment sourced from a total of 8254 data points sourced from a total of six studies and four clinical populations and established with the original serum creatinine values actively recalibrated using

the Roche enzymatic approach [18]. The CKD-EPI equation is inclusive of the serum creatinine with the issues of gender, race and age on a natural scale. It is hence significantly four distinct equations for the whites with other four African-Americans where a distinct factor is preferred and adopted.

Despite the effectiveness of the CKD-EPI in implementing their roles effectively, it is evident that their parameters have been questioned in the past. This means that the questioning of the equation is in the areas of the patients with diabetes. For instance, it has been noted that the equation is based on presenting a poor performance among the diabetic patients possessing a broad range of the renal functioning with their operation being presented as worse as opposed to the MDRD equation [19]. Additionally, the limitation of the account is evident from the misclassification of the patients in the 8 and 10% of the different cases in their use of the CKD-EPI. This is coupled with the inexistence of international standardized calibrator which has a direct limitation on the use of the equation. Hence, these limitations and their inaccuracy in terms of their additional costs, its adoption is dependent on available evidence that it has a significant implication in improving the overall clinical outcomes. This means that as a consequence of the inter-assay differences, the prevalence of the CKD is found to be varying based on the assay used with the calibration standardization being essential. A reference strategy for the Cystatin C is still not available but the standardization equation is still available.

Cystatin C-based equation

Cystatin C is a protease inhibitor and a low-molecular weight protein. It is produced within all the nucleated cells of the human body at a constant rate and is freely filtered within the proximal renal tubules [19]. The concentration and extent of serum cystatin C is usually determined by the process of glomerular filtration and is usually considered an internal surrogate marker in terms of identifying and interpreting kidney function [17]. The estimation of GFR by incorporating both serum creatinine and cystatin C is also widely practiced across the world [20]. As expressed by Kilic et al. [21] in the Cystatin C approach, the Cystatin C is being used as a marker for the analysis of the performance of the patients’ kidney function. The use of serum creatinine and cystatin C approach also proves extremely effective in terms of obtaining accurate and exact estimations of the GFR. The deficiency of standardized calibrator limits the use of cystatin C approach in terms of estimating the GFR and analyzing renal function of those patients. According to Zhang et al. [22], the Cockcroft-Gault equation is used in calculating the GFR in the adult’s population. Nevertheless, it is not based on the issue of age and body weight and showing large errors in the old patients and hence inaccuracy of this equation. Cystatin C is preferred as is effective and unaltered in most of the inflammatory conditions or other disorders of metabolism [19]. A summary of the different advantages and disadvantages of the evaluated formulae is as shown in **Table 1**.

Table 1. Different formulae to estimate GFR: Advantages and disadvantages.

	Advantages	Disadvantages
MDRD Equation Approach	Acceptable broadly among the Caucasian and African American population between the ages of 18 and 70 suffering from impaired kidney function.	Use of this formula in those patient groups leading to errors in GFR estimation which are characterized by poorer agreement with measured GFR for ill hospitalized patients as opposed to the community-dwelling patients for instance those with near normal GFR.
CKD-EPI Equation Approach	Equation inclusive of factors of age, gender, and race allowing the providers in observing the CKD present despite creatinine concentration appearing to fall within or just above the normal reference interval.	Equation only applicable when the renal function is stable with the serum creatinine values sourced while kidney function is changing does not offer accurate estimates of kidney function.
Cystatin C Approach	Equation applicable in assessing kidney function when the patient’s basal creatinine production is very abnormal. This is the issue with the patients with extreme body size or muscle mass or with unusual dietary intake.	Formula not applicable in patients who have acute diseases such as malignancy, HIV infection or inflammation.

CONCLUSION

This review has focused on the potential of biomarkers to diagnose renal graft dysfunction in the early stages of renal transplantation and the use of equations to accurately estimate GFR. Estimation and analysis of the GFR is based on the plasma levels of creatinine and usually influenced largely by the patients' muscle mass. The most common approaches being used worldwide in terms of estimating relative GFR rate include CKD-EPI equation approach, MDRD equation approach and cystatin C approach. Hence, an appropriate estimation of the GFR possesses undeniable importance within cases of kidney transplantations in terms of early diagnosis of acute kidney injury. This is informed by the fact that GFR estimate is more for the long term assessment of the renal function as the equations are not designed to be used when there is a rapidly changing creatinine.

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