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Measure and risk: Cystatin C, Creatinine and Controversy in CKD

Kate I. Stevens¹,² and Jennifer S. Lees¹,²

¹School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK
²The Glasgow Renal and Transplant Unit, Queen Elizabeth University Hospital, Glasgow, UK

Introduction

How best to accurately measure kidney function remains a contentious issue and it is one which this editorial does not attempt to resolve. However, an understanding of the controversy is necessary to appreciate the relative merits and shortcomings of both cystatin C (CysC) and serum creatinine (sCr) as the basis for estimating glomerular filtration rate (GFR) and thus kidney function in particular scenarios.

Why accurate GFR measure matters?

Identifying chronic kidney disease (CKD) is important because CKD confers an increased risk of adverse clinical outcome; most notably cardiovascular (CV) disease, end stage kidney disease (ESKD) and mortality (1). These risks increase with CKD progression and risk stratification is permitted by accurate measure of GFR. Reliable identification of CKD may allow risk modification. On the other hand, inaccurate GFR measures may result in mislabelling and subsequent health inequity with both financial and social sequelae.

Beyond risk stratification, accurate GFR measure allows for precision in relation to dosing of particular medications. In certain scenarios – eg the use of some chemotherapy agents – inaccurately measuring GFR may not only result in under/over dosing, it may preclude treatment altogether, with potentially catastrophic consequences (2).

In other populations, for example potential living kidney donors, reliably measuring GFR is paramount because failing to do so could result in acceptance of individuals with reduced GFR or rejection of potential donors who in fact do have acceptable kidney function for donation. Again, this mis-categorisation can have devastating consequences.
Creatinine and Cystatin C as measures of GFR

A substance which is freely filtered from plasma and not secreted into the tubules nor reabsorbed back into the plasma should have a clearance equivalent to GFR. Measured GFR (mGFR) is based on this principle of clearance and by measuring the plasma concentration and urinary excretion of exogenous substances which fulfil this description; for example inulin or iohexol, GFR can be calculated ‘exactly’(3). To do this in in every day practice is time consuming, inconvenient and generally impractical. Alternative calculations are preferred using GFR equations based on sCr, CysC or both to provide an estimated (e) GFR (4). Both sCr and CysC are flawed markers of kidney function due to non-GFR determinants, yet in fact, there is no perfect measure of kidney function because even ‘gold standard’ mGFR displays considerable measurement variability (5).

Creatinine and CysC are small molecules (molecular mass 0.11kDa and 13kDa respectively) measurable in the serum and filtered unchanged at the glomerulus (5,6). Creatinine is also secreted by proximal tubule cells (PTC) and so creatinine clearance exceeds GFR. Medications, eg trimethoprim, which block creatinine secretion at the PTC will increase sCr levels but will not affect GFR. Creatinine is a metabolite produced as a result of protein and muscle breakdown whereas CysC is produced constantly by all nucleated cells (and it is therefore not dependent upon muscle mass). Both are affected by age and sex although CysC to a lesser extent (5). GFR may also be affected by age and sex. One of the main reasons sCr and CysC are flawed measures of kidney function is that they are both affected by ‘non-GFR determinants’ - factors which do not influence GFR. Muscle mass, protein consumption, physical activity and ethnicity may all impact sCr whilst steroid use, thyroid disease, diabetes, systemic inflammation and adiposity affect CysC levels (5,7–10).

The performance of either sCr or CysC to estimate GFR is likely to vary substantially by age, sex, level of kidney function and degree of exposure to these other factors which affect non GFR components. Equations to estimate GFR which include both sCr and CysC (eGRcr-cys) seem to better reflect GFR presumably because they balance out non-GFR determinants (4).

Creatinine and Cystatin C as estimators of risk

Identifying, accurately, those with CKD and an increased risk of adverse clinical outcome is of paramount importance when considering GFR measure. Shlipak et al performed a meta-
analysis of 11 studies with more than 90,000 participants – with and without CKD - and found that using CysC to estimate GFR either alone or in combination with creatinine, detected an increased risk of death which was not identified by eGFR equations relying on sCr measures alone (11). A similar association, although to a lesser extent, was seen with risk of ESKD. Subsequent large-scale studies confirm that CysC detects a significant subgroup of patients with CKD at high risk of adverse outcome, including CV disease, and who fail to be identified by eGFR equations relying solely on sCr (12,13). Possible explanations for this include that the non GFR determinants of CysC like the presence of systemic inflammation, obesity or diabetes are also associated with CV and mortality risk. Additionally, it remains plausible that CysC in itself is a biomarker, predictive of outcome, independently of its association with GFR.

In support of this, CysC plays a role in cardiac remodelling and atherosclerosis and elevated levels in the general population are known to correlate with CV disease and death (14).

**Cystatin C as a measure of GFR in kidney transplant recipients**

CV disease is the leading cause of death in kidney transplant patients and risk factors include graft function. Thus, the same arguments for reliable and accurate measure of GFR hold for this patient population.

In studies of kidney transplant recipients undertaken prior to the creation of the standardised CKD-EPI equations using CysC, a systematic review, including 10 studies, found significant discrepancy in the performance of equations estimating GFR based upon CysC (15). Using CKD-EPI formulas, a single centre study of more than 1000 stable kidney transplant patients found that whilst the CysC based eGFR (eGFRcys) equation exhibited higher degrees of bias and underestimated mGFR, it was much more closely associated with CV risk factors compared with a sCr based equation (eGFRcr) (16).

In the kidney transplant population, CysC seems to perform less well as a measure of GFR compared with sCr. The overlap of non GFR determinants of CysC (obesity, diabetes, inflammation) and CV risk factors mean that it may perform better as a prognostic factor for CV events and mortality. In the FAVORIT trial, reduced eGFR by CysC and sCr based equations was associated with increased of CV events. After adjustment for other CV risk factors, eGFRcys remained an independent predictor of CV events but eGFRcr did not (17).
Measurement of CysC may also have a predictive role in the early identification of delayed graft function in this patient cohort (18,19).

**Cystatin C as a marker of risk in kidney transplant recipients**

In this issue of ‘Nephrology, Dialysis and Transplantation’, Keddis et al explore the association between GFR assessment, based on mGFR and eGFR using sCr and CysC (including eGFRcr-cys), and outcome in more than 1000 stable kidney transplant recipients (20). The primary outcome measures were graft failure and a composite outcome of CV event or death. On univariate analysis, lower GFR by any measure (mGFR, eGFRcr, eGFRcys, eGFRcr-cys) associates with both graft failure and CV event/ mortality. When adjusting for mGFR, lower eGFR using sCr – eGFRcr – is no longer associated with either graft failure or CV event/mortality but lower eGFR using CysC based measures (eGFRcys and eGFRcr-cys) remains significantly associated with both endpoints. These relationships largely hold true whether GFR is categorised or measured continuously.

Therefore, if mGFR is unavailable eGFR using sCr is more accurate than eGFR using CysC to determine clinical outcomes due purely to reduced kidney function in the kidney transplant population. In ‘real life’ clinical outcomes are not only dependent upon kidney function and in this population, eGFRcys is superior to eGFRcr to predict outcome. The superiority of CysC based eGFR comes from the non-GFR determinants – if adjusting for mGFR, the association between eGFRcys and CV events/mortality is the same as the unadjusted measures (HR(CI) 1.49 (1.32-1.69) ‘v’ 1.43 (1.34-1.54)).

The implication of course being that the non-GFR determinants contribute more to CV events/mortality than does GFR. Why? There are various possible explanations some, discussed by the authors, include hypoalbuminaemia (as a marker of inflammation), diabetes, proteinuria and obesity. An important oversight is exposure to steroid treatment. In the kidney transplant population, where the vast majority will have ongoing steroid exposure, this is highly likely to have contributed to the main findings. In a dose dependent manner, exposure to steroid elevates CysC levels (10). Kleeman et al show a steroid dependent increase in CysC levels and consequent recruitment of TREM+ macrophages with various consequences including inflammation, atherosclerosis and tumour growth (21). CysC is therefore likely to be disproportionately elevated in the kidney transplant population and discrepant with creatinine.
Conclusion

There is no perfect measure of GFR and the performance of sCr and CysC to estimate GFR is likely to vary substantially by population – age, sex, level of kidney function, exposure to factors which affect non-GFR determinants. The work from Keddis et al highlights that perhaps sCr and CysC should be considered for different purposes in kidney transplant recipients: the former to estimate GFR and the latter to estimate risk. Seeking to minimise steroid exposure is sensible and not just in the context of effects on CysC. Notably steroid minimisation is not without challenge in a kidney transplant population where organs are in short supply and the price of rejection and graft loss is high. Finally, there remain concerns about the availability of CysC assays, the lack of standardisation and the cost.


Figure 1 Methods of measuring GFR, why it matters, what affects eGFR and which eGFR marker when