Chronic kidney disease: towards a risk-based approach

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ABSTRACT

Chronic kidney disease (CKD) affects 8–16% of adults worldwide and is associated with multiple adverse outcomes. It includes a heterogeneous group of conditions with widely varied associated risks; risk stratification is therefore vital for clinical management. Use of the CKD Epidemiology Collaboration (CKD-EPI) equation to estimate glomerular filtration rate (GFR) instead of the Modification of Diet in Renal Disease (MDRD) equation will reduce, though not eliminate, over-diagnosis of CKD. Cystatin C is recommended as an alternative measure of GFR but is not yet widely used. A new classification system for CKD, which includes GFR and albuminuria, has been endorsed by the National Institute for Health and Care Excellence to aid risk stratification and a recently validated formula, requiring only age, gender, eGFR and albuminuria, is useful to predict risk of end-stage kidney disease (ESKD). A risk-based approach will facilitate appropriate treatment for people at high risk of developing ESKD while sparing the majority, who are at low risk, from unnecessary intervention.

KEYWORDS: Chronic kidney disease, cystatin C, estimated GFR, KFRE (kidney failure risk equation), risk prediction

Introduction

The publication of a definition and classification system for chronic kidney disease (CKD) in 2002[1] prompted a welcome increase in awareness of kidney disease, which resulted in important developments in the UK – including universal reporting of estimated glomerular filtration rate (eGFR) with every serum creatinine measurement, publication of guidance on the diagnosis and management of CKD by the National Institute for Health and Care Excellence (NICE) in 2008 and inclusion of performance indicators for management of CKD in the Quality and Outcomes Framework (QOF) for GPs. Although controversial in some aspects, these developments have been credited with contributing to a stabilisation in the number of people requiring renal replacement therapy (RRT) for end-stage kidney disease (ESKD) in the UK and a reduction in the proportion being referred late or as an emergency.[2] Nevertheless, there remains some concern that the current approach results in overdiagnosis and severe doubts have been expressed about the relevance of CKD as currently defined.[3] As a result, there has been a shift in focus away from CKD in the UK over the last few years with removal of most of the CKD indicators from the QOF. In addition, updated guidance on CKD published by NICE in 2014 has gone largely unimplemented, resulting in limited adoption of several new recommendations.[4] Many of these recommendations relate to developments that will improve diagnosis and risk stratification in people with CKD, addressing the very issues that have raised concerns in the past. This lack of adoption means that the opportunity to improve the management of people with CKD is being lost. This paper will review recent developments with respect to CKD and focus particularly on those that will assist with risk stratification, which is vital for identifying the minority of people with CKD who will benefit from intensive management and referral to a nephrology service while sparing the majority from unnecessary treatment and intervention.

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Epidemiology

Studies from around the world have confirmed that CKD remains a global problem with a reported prevalence in adults that varies from 8–16%.[5] Despite the progress made in improving detection and management in some countries in recent years, CKD has increased in the ranking of leading causes of global deaths from 27th in 1990 to 18th in 2010.[5] The best published data to estimate the prevalence of CKD in the UK are derived from the Health Survey for England studies of 2009 and 2010, which included a random sample of adults in England and found a prevalence of 5.2% for CKD stages 3–5 and 7.1% for CKD stages 1–2. Albuminuria was detected in 8% of participants.[6]

New methods to estimate glomerular filtration rate

The CKD-EPI equation

From the time of its publication, it was clear that the first equation to be widely adopted for the estimation of GFR by laboratories, the Modification of Diet in Renal Disease (MDRD) study equation, tended to underestimate GFR at values above 60 mL/min/1.73 m^2.[7] This is important because the current definition of CKD allows the diagnosis to be made if the GFR is <60 mL/min/1.73 m^2 (on at least two occasions at least 90 days apart) in the absence of any other markers of kidney damage. Use of the MDRD equation may therefore yield GFR estimates of less than 60 mL/min/1.73 m^2 in individuals who actually have normal GFR and, thus, may result in an overdiagnosis

of CKD. Several alternative equations have been developed to estimate GFR from serum creatinine but an equation developed by the CKD Epidemiology Collaboration (CKD-EPI)[8] appears to perform the best and was recommended by NICE in 2014 to replace the MDRD equation. Comparison with the MDRD equation showed that the CKD-EPI equation was more accurate and associated with greater precision and less bias, particularly at higher GFR values. Application of the CKD-EPI equation to data from the National Health and Nutrition Examination Survey (NHANES) reduced the prevalence of CKD in the US general population from 13.1% (when the MDRD equation was used) to 11.5%.[8] Despite the NICE recommendation, many laboratories in the UK still use the MDRD formula, possibly because of concern that changing the equation would cause confusion and uncertainty among healthcare providers and patients. A strategy is needed to overcome these problems and promote implementation of the CKD-EPI equation. Education and communication should form a vital part of such a strategy and reporting of both MDRD and CKD-EPI eGFR values for a transition period should be considered.

Cystatin C

It is widely recognised that serum creatinine is an imperfect marker of GFR because the concentration may be affected by factors other than GFR, including age, muscle mass, consumption of meat and some drugs. Alternative endogenous markers of GFR have therefore been sought and cystatin C has been identified as an alternative or complementary to creatinine. Cystatin C is a small peptide produced at a constant rate by all nucleated cells and cleared from the circulation by glomerular filtration. It is therefore not affected by muscle mass or diet. An equation has been developed and validated to estimate GFR from serum cystatin C (CKD-EPI$_{cys}$) concentration and was found to have accuracy, bias and precision similar to eGFR based on creatinine using the CKD-EPI equation (CKD-EPI$_{creat}$).[9] Use of an equation that included both creatinine and cystatin C (CKD-EPI$_{creat\text{-}cys}$) was found to improve precision and accuracy and showed similar bias to GFR estimated from either creatinine or cystatin C.[9] Further research has shown that use of CKD-EPI$_{cys}$ is associated with improved prediction of the risk of all-cause and cardiovascular mortality, as well as ESKD when compared with CKD-EPI$_{creat}$.[10,11] Based on this improved risk prediction, the 2014 NICE guidance recommends the use of CKD-EPI$_{cys}$ to confirm the diagnosis of CKD in people with eGFR 59–45 mL/min/1.73 m^2 in the absence of other markers of kidney damage (principally albuminuria). The guidance specifically recommends that a diagnosis of CKD should not be made if CKD-EPI$_{creat}$ is 59–45 mL/min/1.73 m^2 but CKD-EPI$_{cys}$ is ≥60 mL/min/1.73 m^2. Despite this recommendation, CKD-EPI$_{cys}$ is used in only a minority of centres in the UK because the assay is currently performed by only a small number of laboratories and is more expensive than creatinine assays. In addition, it has become clear that cystatin C concentration may be affected by factors other than GFR, including thyroid disease[12] and inflammation.[13] Further research is being conducted in the UK to investigate the clinical utility of using CKD-EPI$_{cys}$ to diagnose CKD and monitor progression over time.[14]

GFR estimating equations for older people

Concern that the CKD-EPI equations had not been adequately validated in older people led to the development of new equations in a cohort of people ≥70 years of age by the Berlin Initiative Study (BIS). One equation used creatinine only (BIS1) and another both creatinine and cystatin C (BIS2). The new equations were associated with less bias and a lower misclassification rate than the CKD-EPI equations [15] and have subsequently been externally validated.[16,17] However, further studies have shown that the BIS2 equation reclassified more older people to a more advanced CKD category[18] and was inferior to the CKD-EPI$_{creat\text{-}cys}$ equation for predicting adverse outcomes.[18,19] Therefore, current evidence does not support using different GFR estimating equations for older people.

Revised CKD classification system

The original classification system divided CKD into five stages based on GFR and provided a valuable tool to standardise the nomenclature for research and guideline development, but has been criticised because the stages correlated poorly with the risk of adverse outcomes. Large epidemiological studies over the last decade have reported that eGFR and albuminuria are each powerful independent risk factors for multiple adverse events associated with CKD, including increased all-cause mortality, progression to ESKD, cardiovascular events (CVE) and acute kidney injury (AKI).[20–22] These observations prompted the development of a new classification system for CKD that incorporates both eGFR and albuminuria.[23] CKD is divided into GFR categories that correspond to the previous stages (G1–G5) and albuminuria categories (A1: urine albumin to creatinine ratio (UACR) <3 mg/mmol; A2: UACR 3–30 mg/mmol; A3: UACR >30 mg/mmol). To emphasise that CKD may result from a wide range of pathological processes, it is recommended that the classification should be used in combination with the specific renal diagnosis. For example, a patient with diabetic nephropathy, eGFR 52 mL/min/1.73m^2 and UACR 19 mg/mmol would be classified as 'diabetic nephropathy, CKD G3a A2'. Although this system is more cumbersome than the original classification, it offers the advantage that the categories reflect patients' risk of multiple adverse outcomes and it is therefore a useful and simple tool to aid risk stratification in clinical practice. This classification was endorsed by NICE in 2014 but has not yet been widely adopted in the UK. Further education regarding the benefits of the new classification system, leadership in adopting and reporting the new classification by nephrology units and modification of electronic patient records to incorporate the new system will all help to increase its use.

Risk prediction in CKD

CKD affects 8–16% of adults worldwide and the prevalence rises to almost 50% after the age of 70 years.[24] It is important to appreciate, however, that CKD is an extremely heterogeneous group of conditions and that the associated risk of adverse outcomes varies widely. Population-based studies have reported that the majority of people with CKD are at low risk for progression to ESKD but are at increased risk for future CVE.[25] Thus, robust risk prediction is fundamental to the management of CKD because it enables clinicians to identify people who are

at high risk and may require more intensive therapy or referral to a nephrology service while sparing people at low risk from unnecessary intervention or treatment.

Renal risk

Much progress has been made in developing tools to predict the risk of progression to ESKD. One equation, the Kidney Failure Risk Equation (KFRE), was developed in a retrospective cohort of Canadian patients referred to a nephrology service and included age, gender, GFR estimated using CKD-EPI$_{creat}$, albuminuria, serum calcium, serum phosphate, serum bicarbonate and serum albumin to predict the risk of ESKD at 2 and 5 years.[26] The full 8-variable KFRE achieved excellent discrimination in the development cohort (C statistic = 0.917) and validation cohort (C statistic = 0.841) and a 4-variable KFRE that included age, gender, eGFR and albuminuria also performed well (C statistic = 0.910 and 0.84 in development and validation cohorts, respectively). The KFRE has recently been validated in a large dataset (CKD Prognosis Consortium) that included 721,357 individuals with CKD stages 3–5 from 31 cohort studies in North America, Asia, Europe and Australasia. The 8-variable KFRE performed well with a C statistic of 0.89 at 2 years and 0.86 at 5 years but the 4-variable KFRE achieved slightly better discrimination with a pooled C statistic of 0.90 at 2 years and 0.88 at 5 years. Calibration was good in North American cohorts, but the KFREs overestimated risk in some non-North American cohorts. Addition of a calibration factor improved calibration in 12/15 and 10/13 non-North American cohorts at 2 and 5 years, respectively.[27] The 4-variable KFRE, therefore, represents a simple and well-validated tool for risk stratification in clinical practice. The investigators have created a helpful website that gives additional information and provides an online calculator to estimate the risk of ESKD (**http://kidneyfailurerisk.com/**). As the four variables required are readily available, it should be relatively simple to add this equation to laboratory and clinical information systems so that the risk is calculated automatically. It should be noted that the KFRE was developed and validated using CKD-EPI$_{creat}$ and it may therefore not perform as well if used with eGFR derived from the MDRD equation.

Cardiovascular risk

As discussed, people with CKD are at substantially increased risk of CVE but unfortunately cardiovascular risk prediction tools developed in general populations, such as the Framingham risk score, substantially underestimate cardiovascular risk in people with CKD.[28] The QRISK2 equation sought to address this problem by incorporating CKD as a risk factor but included it only as a binary term[29] (CKD present or not) whereas subsequent studies have emphasised that eGFR and albuminuria are each independent risk factors for CVE. A 2015 meta-analysis by the CKD Prognosis Consortium has illustrated this by showing that eGFR and albuminuria, independently and in combination, significantly improved the discrimination of Framingham risk factors in predicting CVE in general populations and people known to have CKD.[30] To date, however, there is no validated risk prediction tool that adequately accounts for the increase in cardiovascular risk associated with CKD. Until better tools are developed, all people with CKD should be regarded as high risk and efforts made to reduce this risk with treatment of hypertension, statins and lifestyle improvement. Further research is required to define the optimum treatments to reduce cardiovascular risk associated with CKD and the development of improved methods to assess cardiovascular risk is important to facilitate further research in this regard.

Conclusion

CKD remains a significant challenge to the health of large numbers of people worldwide and is associated with multiple adverse outcomes. However, the risk is variable and risk stratification is therefore essential for optimal management. Substantial progress has been made in recent years to improve the accuracy of GFR estimation and adoption of the CKD-EPI equation to replace the MDRD equation will reduce (but not eliminate) overdiagnosis of CKD. The revised classification system for CKD, endorsed by NICE, provides a simple means of risk stratification and the 4-variable KFRE represents a well validated tool for more accurate prediction of the risk of progression to ESKD. A robust tool to adequately predict cardiovascular risk in people with CKD is still required. ■

Conflict of Interest

The author has no conflict of interest to declare.

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