Predicting outcomes in CKD: the importance of perspectives, populations and practices

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The problem of chronic kidney disease (CKD) has been brought into focus over the last 7 years since the publication and dissemination of the KDOQI definition, evaluation and classification of CKD guidelines, and the implementation of eGFR reporting by laboratories in numerous jurisdictions [1]. Together these two ‘events’ have substantially increased awareness about and focus on CKD in both clinical and academic spheres. Concerns and issues have been raised as to the validity of the stages in all populations, the need for more refinement and the possibility of misclassification and inflated estimates of CKD in populations based on eGFR equations [2,3]. These discussions aside, the ability to report or calculate eGFR has improved the identification of abnormalities of kidney function in persons around the world, and stimulated substantial research into the validation of the equations in different populations, and prediction models for progression to renal replacement therapy (RRT) or death. The increasing appreciation of CKD diagnosis models for progression to renal replacement therapy (RRT) or death. The increasing appreciation of CKD as a multiplier of risk, and as more common in high-risk populations with CVD and diabetes, has helped to focus attention on these patient groups, and may well permit avoidance of adverse events due to better identification [4,5].

The paper by Conway et al., in this edition of the journal, examines the outcomes of 396 patients with stage 4 CKD referred to nephrology clinics in the UK using electronic databases to determine important outcomes of death, dialysis and rates of progression [6]. The major goal of the study was to identify factors that predict outcomes in CKD patients and whether low-risk patients could be managed in primary care. The authors examined an elderly cohort of patients (71% over the age of 65) in a national health care system, with a substantial primary care infrastructure support. The importance of this study is that it describes outcomes of those patients, who were referred to nephrology care prior to the publication of the KDOQI, and subsequent UK Guidelines for CKD care and before the nationwide eGFR reporting strategy was implemented [7]. In this referred elderly cohort, those over the age of 74 progressed at a rate of $\sim 0.86$ ml/min/1.73 m$^2$/year, substantially slower than those in the other age groups of $<65$ or between 65 and 74. Interestingly, proteinuria was less with increasing age at referral, and median creatinine was lower in older patients, though eGFR was $\sim 22$ ml/min/1.73 m$^2$.
and not different between age groups. There were no differences in age of those opting for conservative rather than dialytic management (5% of the cohort opted for conservative management). Interestingly, those older patients with a diagnosis of GN or vasculitis or with baseline eGFR of <20 ml/min/1.73 m² were most likely to progress, and the need for RRT was relatively low in the elderly group. No differences in eGFR at the time of dialysis start, nor in eGFR at the time of death were observed within the different age groups. Overall, those over the age of 75 were more likely to die than commence RRT. Almost 25% of the cohort was discharged to primary care with stable kidney function, and most died prior to needing RRT. The authors conclude that those at low risk of progression can be identified and discharged safely to primary care with an active management plan.

The study used electronic databases to identify the patients, and additional computerized renal unit and patient administration databases were used for follow-up. Northern Ireland and South East Scotland cohorts were used, and were similar in most aspects. The rate of referral was noted to increase dramatically with age up to 80 years, then declining in the very elderly.

There are some important points made by the authors in the discussion of the findings. Firstly, the fact that despite low levels of progression to RRT, the absolute amount of intrinsic renal disease is higher with increasing age. This is associated with hypertension and other vascular diseases, and thus likely represents true pathological processes such as renal hypoperfusion, atherosclerosis, hypertension and impaired cardiac function, all of which contribute to glomerulosclerosis. The concept has perhaps been overlooked in recent debates of the utility of the equation in elderly. Irrespective of progression rates, it is important to recognize impaired kidney function in older individuals. The second fact, related to the first, is that low eGFR in the elderly is associated with co-morbidities that are likely to lead to death before the need for RRT, whereas low eGFR in younger individuals is more likely due to intrinsic renal disease and thus likely to progress to RRT. Again this helps clinicians to differentiate the arguments regarding validity of the equation in the elderly versus meaning of lower eGFR in the elderly. Whether the disease leads to the outcome of RRT or of death does not define the presence or absence of the disease.

The paper describes well the outcomes of Caucasians in the UK who are referred to nephrologists, and are seen at least once. The cohort was assembled in a pre-QOF initiative and UK Guidelines for CKD care era, and so may not reflect current referrals [8,9]. Since the current equations are not robust above the age of 75 and may well underestimate eGFR, it is possible that more referrals of the elderly have been forthcoming. However, as this study shows, the elderly progress slowly, and are more likely to die than begin RRT; thus, the argument that eGFR reporting will increase dialysis rates is likely unfounded. Others have reported similar findings [10,11]. This study represents the ‘worse’ case scenario with respect to outcomes, and yet identifies a 25% stability not requiring nephrology follow-up, and mortality as a more likely outcome than dialysis. This information is helpful in guiding clinical practice.

The importance of defining the perspectives, populations and clinical practice differences is key to understanding and appropriately contextualizing CKD, and to understanding the condition more completely.

The use of electronic databases to identify individuals at risk or with a condition is becoming more common. The use of large databases to understand population demographics and outcomes is highly valuable, and the definition of the cohort studied is essential. The health care system in which patients are identified is also important. The UK system is different to many European and American health care systems, and more similar to Canadian and Australian systems. We recently have reported similar outcomes in a large cohort of referred patients [11]: those of advanced age and little proteinuria despite low eGFR are more likely to die than to progress to RRT.

The clinical practice in the UK, and other countries with strong primary care infrastructure, not only permits a long-term follow-up of the patients but also a safety net by which to ensure an easy re-entry into the specialist system. Can the same outcomes be expected in systems without primary care infrastructure? It is not possible to extrapolate, but this report does stimulate more research into similarly defined cohorts, in different health care systems.

The implementation of reporting eGFR estimates in the elderly has identified large groups of patients with lower eGFR, in stages 3 and 4 CKD [12]. The importance of the current study is the observation that they do in fact have kidney disease albeit mostly from cardiovascular morbidity, but that there are reliable factors that can help to predict outcomes (proteinuria, anaemia, initial GFR). Most importantly, the stability of over one-quarter of the population gives comfort to the nephrologists regarding being overwhelmed by large numbers of geriatric referrals.

The argument used by many to dissuade the use of eGFR reporting and use of the classification system is that it identifies too many people who are old and will not progress to RRT. I would like instead to ask my nephrology colleagues to consider that low eGFR in the elderly is a marker of co-morbidities, which in aggregate are severe enough to lead to a cascade of sclerosing processes in the kidney. The insults are not of sufficient severity to generate rapid or consistent progression of CKD to the point of requiring RRT, but do mark for increased probability of dying. Thus, instead of thinking of lower eGFR as a surrogate for aging, we should conceptualize it as a proxy for co-morbidity and adjust our treatment and diagnostic plans accordingly. Patients with lower eGFR are also at risk for AKI, adverse effects of drugs and acute changes in effective circulating fluid volume due to their reduced renal reserve [13].

It is important to increase our precision and ability to predict outcomes in CKD so that appropriate resources, expectations and systems can be put in place that optimize individual patient outcomes and health care system functioning. This study, within the context of other published literature, helps us to focus on the importance of identifying and describing populations of interest, and characterizing clinical practices and care systems and the interaction of these on patient outcomes. The perspective of the nephrologists, primary care physicians and patients need to be
Three articles published in the New England Journal of Medicine at the beginning of 2008 demonstrated that the induction or development of mixed chimerism in kidney or liver transplant recipients can lead to long-term donor specific tolerance following transplantation, irrespective of whether the chimerism is sustained or not [1–3].

Chimerism occurs when foreign (donor) haematopoietic cells are present in an individual. Complete chimerism indicates that all haematopoietic cells (100%) are derived from a donor stem cell inoculum (for example, following myeloablation and transplantation of donor haematopoietic cells), whereas in mixed chimerism donor cells of multiple lineages constitute a varying part of the total haematopoietic cells [4–6].

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References


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Tolerance in renal transplantation: is mixed chimerism the missing link?

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