The Next Step in Chronic Kidney Disease Staging: Individualized Risk Prediction

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Chronic kidney disease (CKD) stage-based classification has been used as a framework for clinical practice, public health, and research for the last twenty years (1). Categorization of risk, utilizing estimated glomerular filtration rate (eGFR) and proteinuria measurement, has become an important part of CKD's identification and management (2). More advanced stages of CKD are associated with higher risk of end stage kidney disease, cardiovascular and all-cause mortality (2). Within this paper, we briefly describe the current CKD staging system and its limitations, and propose the addition of individualized risk estimation to supplement the system.

The KDIGO CKD classification system was introduced after the development of creatinine based estimating equations for glomerular filtration rate (eGFR) and initially comprised five stages (2). Stages 1 and 2 also require the presence of other evidence of kidney disease, such as a structural abnormality, hematuria or proteinuria, to diagnose CKD. Stage 3 was subsequently divided into stages 3a and 3b and in 2011 the classification system was further extended to include proteinuria and etiology of CKD (2).

The staging system has facilitated assessment of the burden of CKD through mapping stages to risk of adverse outcomes at a population level. This has enabled increased awareness and resource allocation for CKD, utilization for referral pathways and management for patients.

However, critics of the system argue that the eGFR based stages in the current system do not account for an age related decline in kidney function (3). Currently, for individuals with reduced eGFR (<60 ml/min/1.73m^2), CKD staging allows their risk to be clustered into a maximum of twelve groups. However, with regards to the risk of progression to kidney replacement therapy (KRT), the current classification does not allow identification of the subgroup most likely to progress to KRT. Within-cluster patient heterogeneity can be substantial, especially at the border between categories. Figure 1 illustrates this in further detail. Essentially, when comparing relative risk in current CKD groups it is far more appropriate to compare an individual at the "center" of the cluster i.e. an individual with eGFR of 37 ml/min/1.73m^2 and ACR of 165 mg/g for stage 3bA2 compared to an individual with an eGFR of 22 ml/min/1.73m^2 and an ACR of 18 mg/g for stage 4A1.

We therefore propose changes to the current CKD staging system to better reflect individualized KRT risk for individuals with CKD. We believe that individualized risk prediction based on the Kidney Failure Risk Equation (KFRE) should supplement the current categorization (4).

Whilst cardiovascular disease has over 300 models and little consistency of use within or between countries (5), KFRE has been thoroughly evaluated in multi-national cohorts and established a foundation for the implementation of KFRE as a truly global KRT risk prediction tool (6,7). In a recent independent, external validation study, seven groups of models were identified (8). Model performance was similar across these, but KFRE was the most extensively validated risk prediction tools of the seven and one of only two using the same predictors as the current KDIGO staging system. This study provides an excellent summary of these models and detailed discussion of them is beyond the scope of the current article. Therefore, KFRE is probably the most appropriate model to form the basis for identifying subgroups with differing KRT prognosis that facilitates clinical decisions to improve patient outcomes (9).

For the rest of the article we refer to the intra-individual risk for a 70 year old female, using the North American calibrated 5-year risk 4-variable (age, gender, eGFR and urine ACR) KFRE model as an exemplar; similar results and conclusions could be drawn regardless of the age, gender or location of the patient. The possible spectrum of risk for this individual is shown in Table 1.

Stage	A1, <30mg/g	A2, 30-300mg/g	A3, >300 mg/g
3a, 45-59	<0.1% to 1.2%	0.2% to 3.3%	0.7% to 9.0%
3b, 30-44	0.3% to 6.1%	1.3% to 16.2%	3.7% to 39.3%
4, 15-29	1.5% to 28.2%	6.8% to 60.9%	17.9% to 93.0%
5, <15	7.7% to 51.5%	31.0% to 87.1%	65.0% to 99.7%

Table 1: Spectrum of potential kidney replacement therapy five year risk for 70 year old women using the four variable North American calibrated KFRE. Upper limit for Proteinuria Stage A3 – 3000 mg/g, lower limit for Proteinuria Stage A1 – 1 mg/g, lower limit for eGFR Stage 5 – 8 ml/min/1.73m^2

The wide range of risk in each category indicates some practical issues in the delivery of individualized care:

1. Current risk categorization can only ever provide a maximum of twelve categories of risk with great emphasis on small arbitrary changes such as an eGFR declining from 30 to 29 ml/min/1.73m^2, leading to "progression" of disease from 3b to 4, often of great concern to patients despite the minor change in absolute risk.
2. It is possible for the example individual with stage 3aA1 disease (1.2% risk) to have a similar risk to an individual with stage 4A1 disease (1.5%), depending on their ACR level within the stage despite a more than 15 ml/min/1.73m^2 difference in eGFR.
3. Within categories' intra-patient risk can range in magnitude by more than 10-fold, for instance risk for the example individual for stage 3bA2 risk varies between 1.3% and 16.2%. Where age and gender vary too, the risk range can be up to 40-fold.
4. CKD staging and maintenance provides a great administrative burden that either leads to CKD coding being inaccurate or diverts care from cardiovascular risk factor management or ACR measurement and preventing the need for KRT.

As KFRE has been shown to have excellent validity for an eGFR of <60 ml/min/1.73m^2, but not yet for ≥60 ml/min/1.73m^2, we propose the following in relation to KRT risk:

1. 5 year 4-variable KFRE risk, with appropriate local re-calibration, to be reported as part of CKD staging as a supplement to eGFR and albuminuria based stage and etiology.
2. The current classification for CKD stages 1 and 2, including the need for other evidence of kidney pathology such as proteinuria, to be continued until individualized risk prediction tools that predict intermediate progression outcomes for these categories (e.g. 40 % decline in eGFR) are developed and undergo validation studies.

There will be implementation challenges to this change but we believe our proposed system will provide net benefit to individuals with CKD in all types of healthcare systems and guide management with regards to identifying those at higher risk of progression, which can then inform timely referral to secondary care (9). The system would also facilitate improved communication of KRT risk to individuals and their carers. Perhaps the biggest barrier to adoption of the system will be regular measurement of urine ACR, something which also remains a limitation of the current KDIGO system. Whilst measurement of ACR may occur on an annual basis in 80% of individuals with CKD and diabetes mellitus, the figure is close to 30% in those without diabetes. Our proposed system though would potentially act as a facilitator for improved ACR measurement by placing further onus on clinicians to measure ACR in order to be able to provide individualized KRT risk and/or by referral guidance including KFRE based criteria.

The current KDIGO classification system, KFRE and the other identified models all share similar limitations when used for individualized care. The inherent limitations and lack of precision of creatinine-based eGFR and ACR remains a significant constraint of the current KDIGO system, KFRE and all of the other six identified models. Implementation as a supplement to the KDIGO staging system of one of the other six models identified would provide the additional challenge of routine collection, particularly in primary care, of variables used by the models, such as serum phosphate. For this reason despite some minor improvement in prediction we would not advocate the 8 variables KFRE as a supplement to the KDIGO staging system.

More extensive validation of KRT risk prediction for distinct disease groups such as glomerulonephritis and polycystic kidney disease are required for KFRE-style risk prediction. Therefore, as with the current staging system, we would suggest caution when using KFRE, or any of the other six risk prediction tools, in individuals with these etiologies. Disease specific risk tools, such as in IgA nephropathy, could be consider as alternatives where available (10). Longer KRT prediction timeframes for some specific conditions and high levels of proteinuria, such as category A3, may be required to re-enforce the importance of attenuation of proteinuria for long term risk reduction of needing KRT. The use of KFRE, which incorporates age, also provides a compromise to address concerns raised regarding potential "age-adapted" CKD classifications which we believe would be difficult to appropriately implement within routine clinic practice.

Whilst we focus on KRT risk here, there is ongoing work to incorporate renal function markers into commonly used tools for risk prediction for cardiovascular and all-cause mortality. The work by Grams *et al*. is an important development in this area; this model does predict events for all three outcomes, but was developed in individuals with eGFR <30 ml/min/1.73m^2 (11). We believe that future research should aim to extend Grams *et al's* work to develop individualized risk for KRT, cardiovascular disease and all-cause mortality risk for all stages of CKD. This could then replace the current staging system with an individualized risk-based system for relevant outcomes.

In summary, category-based CKD definitions have served individuals with CKD and their care teams well for the last twenty years, but it is now time to pivot to outcome specific prediction. The implications and management of all conditions, including CKD, should be based on individualized risk and not broad categorization and/or non-modifiable risk factors, such as age. The imprecision of eGFR, and to a lesser degree ACR, remains an intrinsic limitation to the use of KFRE and CKD staging in general for individualized risk prediction and further research to address this issue is required. KFRE-based risk is not a panacea, but it does provide patients and clinicians with more appropriate risk measures for the risk of needing KRT and organizing appropriate care. To paraphrase George Box, the eminent statistician, "all staging systems are wrong, but some are more useful than others".

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Figure Title and Legend

Figure 1: Within CKD category KRT risk heat map for stage 3bA2. Cluster center refers to an individual with eGFR 37 and ACR of 165. 'Risk similar to' other categories refers to those on the peripheries of the respective categories. Median risk is an approximation due to left and right skews of eGFR and ACR population data respectively and non-linear relationships with KRT risk.

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