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A New Clinical Prediction Tool for 5-Year Kidney Transplant Outcome

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The last 20 years have yielded an explosion of prognosis research. A search for “risk prediction” in PubMed yields 283, 792, and 2,821 results from 1992, 2002, and 2012, respectively. The use of decision-making tools in clinical practice has been facilitated by the widespread adoption of electronic medical records and smart phones. Risk calculators are now easily accessible by clinicians through various electronic devices. In kidney transplantation, major improvements in acute rejection rate and short-term transplant survival¹ have shifted focus toward predicting and improving long-term survival.² The leading causes of late transplant loss are death with a functioning transplant and chronic immunemediated transplant dysfunction.^{3,4} Several simple clinical prediction tools for long-term transplant survival generated from readily available clinical and laboratory data have been published recently,^{5–8} and the risk prediction instruments described by Shabir et al⁹ in this issue of *AJKD* fall into this category.

Prediction tools for long-term transplant outcome in prevalent kidney transplant recipients can be divided broadly into models with and without biopsy data. Several published studies show a correlation between protocol kidney biopsy findings and long-term transplant survival. The chronic allograft damage index (CADI) score at 2 years posttransplantation predicts medium-term transplant function using a sum of vascular intimal sclerosis, tubular atrophy, interstitial fibrosis, interstitial inflammation, mesangial matrix increase, and glomerulosclerosis.¹⁰ Other studies have emphasized the value of interstitial fibrosis plus inflammation or subclinical rejection in the prediction of long-term transplant survival.^{11,12} However, limits to protocol biopsies include reproducibility and specificity in a subclinical setting.¹³ Ultimately, opinion about protocol biopsies remains divided, for which the crux of the argument involves risk, cost, and lack of proven long-term benefit versus the potential merit of early detection of subclinical rejection, interstitial fibrosis/tubular atrophy, or recurrent disease.¹⁴

The development of predictive biomarkers in kidney transplantation has been the center of much attention; most notably, the recent study by Suthanthiran et al¹⁵ showed that an increase in a 3-gene urinary messenger RNA signature preempted acute rejection events by weeks. Novel biomarkers also have shown some promise in predicting long-term transplant

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outcome.^{16,17} However, to date, these markers, many of which require specialized laboratory testing, have not proved attractive enough to warrant widespread adoption.

Despite the availability of prediction tools developed to date, the most widely used clinical gauge of transplant survival remains kidney transplant function, estimated using either serum creatinine or one of the many available estimated glomerular filtration rate (eGFR) equations. The ease of implementation using common clinical variables has allowed for eGFR to be adopted readily into routine clinical practice in both general and transplant nephrology. Previous studies have shown an association between kidney transplant function at 1-year posttransplantation or change in function in the first year of transplantation and long-term outcome.^{18,19} However, other studies have shown only a modest, if not poor, predictive capability of early serum creatinine testing for late transplant dysfunction.^{20,21} Furthermore, creatinine-based GFR estimating equations are imperfect measures of kidney transplant function.²²

Shabir et al⁹ have developed multivariable prediction models for 5-year death-censored transplant failure and overall transplant failure using data collected from 651 patients in the United Kingdom at 12 months posttransplantation. The final models contain 6 variables independently associated with death-censored transplant failure, and 7 with overall transplant failure: age, sex, race, eGFR, history of acute rejection, and urine albumin-creatinine ratio in both and serum albumin level in the overall transplant failure model only. The models showed good discrimination, with C statistics of 0.78–0.90 for death-censored transplant failure and 0.75–0.81 for overall transplant failure in 3 outside validation cohorts. The authors used the net reclassification index (NRI) to evaluate the accuracy of their system against the US Renal Data System (USRDS)-based score⁶ (Fig 1) and eGFR to categorize participants into groups of 5%, 6%–10%, 11%–20%, or >20% risk of transplant failure. The NRI is a method of comparing the predictive accuracy of 2 prognostic tools and is calculated as the difference between the proportion of participants correctly and incorrectly reclassified by a new compared to an established predictive tool. The new model resulted in a 30% improvement in reclassification for overall transplant failure compared to the USRDS-based score. Compared to the 4-variable MDRD (Modification of Diet in Renal Disease) Study GFR estimating equation, the new score resulted in a 36.1%–83.0% improvement in reclassification for death-censored transplant failure and a 38.7%–53.5% improvement for overall transplant failure.

The new models share overlapping variables with other recently developed scoring systems, all of which include recipient age and posttransplantation kidney transplant function. The authors highlight their inclusion of urine albumin-creatinine ratio at 1 year posttransplantation; proteinuria is a variable used in only 1 of the 4 recently published prediction systems.⁵ Urine albumin is an easy and readily available test and may be somewhat underused in the transplant population. Albuminuria is a known predictor of progressive kidney function decline in diabetic patients²³ and of both cardiovascular and noncardiovascular death in the general population.²⁴ A strong independent association between microalbuminuria and the outcomes of transplant failure and death was demonstrated in 219 prevalent nonproteinuric transplant patients.²⁵ In another study, urine albumin proved a stronger predictor of transplant failure and GFR decline than proteinuria in

a mostly proteinuric population of kidney transplant recipients.²⁶ In the new model, the inclusion of albuminuria serves to improve predictive performance without adding significant burden to the patient or physician in a routine clinic visit.

An assessment of 5-year risk of transplant loss at a patient's 1-year transplantation anniversary may help focus both patient and physician on optimal future care strategies. The risk information may be used to stratify patients toward more or less intensive surveillance or diagnostic workup. One of the merits of this scoring system is its simplicity. However, physicians will need to interpret and build on an individual's risk score and incorporate other important clinical factors, including sensitization, HLA matching, de novo donor-specific antibody, donor age, and new-onset diabetes after transplantation. Used in this way, the system may prove a useful starting point for decisions about visit frequency, screening biopsy, and immunosuppression regimen.

Improved prediction offers the opportunity to alter therapy, target individuals for further diagnostic testing, motivate lifestyle modification and medication compliance, plan for changes in health status, and manage patient expectations. There is, perhaps not entirely without justification, a certain therapeutic nihilism regarding long-term transplant dysfunction. However, non-calcineurin inhibitor-based immunosuppression regimens, while by no means without problems, are associated with reduced tubular atrophy and interstitial fibrosis,^{27,28} and early identification of those at risk may help identify those who may benefit from a switch. Furthermore, because a significant proportion of all-cause transplant failure is due to death with a functioning transplant (25% of patients in the development cohort), the detection of high-risk individuals may identify patients who would benefit from more intense cardiovascular risk modification. Further studies will need to be carried out to determine whether its routine incorporation into clinical practice improves outcomes. Colin R. Lenihan, MB, BCh Joseph B. Lockridge, MD Jane C. Tan, MD, PhD Stanford University School of Medicine Palo Alto, California

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Figure 1.

The US Renal Data System (USRDS)-based scoring system, recently developed by Kasiske et al,⁶ is now available as a user-friendly online calculator at <http://www.txscores.org/>.

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.