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Clinical Decision Tool Reviews

Review of the Kidney Failure Risk Calculator (KFRE)

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Abstract

The kidney failure risk equation (KFRE) predicts the 2- and 5-year risk of kidney failure in stable patients with chronic kidney disease (CKD) stage 3-5. The 4 and 8-variable models were developed and first validated in two independent Canadian cohorts with CKD already referred to nephrology and where kidney failure was the time to initiation of chronic dialysis or kidney transplantation. Accurately estimated glomerular filtration rate (GFR) and albuminuria (uACR, spot urine albumin: creatinine ratio) are essential components. The model has since been validated in nearly 1 million individuals from over 30 countries and shown excellent discrimination with a C-statistic ranging between 0.88-0.91. The KFRE complements existing eGFR and albuminuria-based CKD staging and risk classification by providing individualized kidney failure risk estimates. It can help improve prognostic communication and guide broader management decisions specifically, referral to nephrology, multidisciplinary CKD management and kidney replacement therapy planning. It should be re-evaluated on subsequent visits as risk may change based on interval exposures and treatment. While model discrimination has been excellent across diverse cohorts, some studies suggest it may need recalibration in certain groups and CKD etiologies.

I. HOW TO USE

When to Use

The KFRE is specifically intended to be used to predict the 2- and 5-year risk of kidney failure requiring kidney replacement therapy for adults with CKD Stages 3–5 (eGFR <60 mL/min/1.73 m^2) based on current laboratory values. The tool may be used in both primary care and nephrology specialty settings to risk-stratify and counsel patients and guide management. It is not intended for use in Acute Kidney Injury (AKI). It should only be used in stable outpatients.

Pearls

The KFRE provides individualized prognostic information regarding risk of progression to kidney failure. The KFRE can assist with estimating prognosis to guide risk factor management, therapy and referral discussions. This can be helpful for identifying patients who would benefit from nephrology and multidisciplinary referral who could have been missed or referred too soon by GFR threshold-based referral alone.

PITFALLS

- The KFRE was primarily derived and validated in CKD patients already referred to nephrology clinics.
- The KFRE was not validated in patients with eGFR >60ml/min/1.73m^2 and should not be used in this population regardless of albuminuria. While the absolute risk of kidney failure in CKD stages 1-2 is generally low, those with albuminuria are at greater risk of kidney failure.
- This tool should not be used in the acute setting and in patients without stable kidney function.
- While the risk tool provides information for broader discussions, clinicians should pursue comprehensive clinical evaluation assessing risk factors and the trajectory of kidney function, follow current guidelines for specific investigative and therapeutic decisions.
- The KFRE provides a snapshot based on current values assuming stability of risk factors. The risk may change based on individual risk factors and depending on the control of the underlying cause and risk factors such as hypertension and diabetes.

- Overestimation of risk occurs in non-North American regions without the application of the regional calibration factor.
- KFRE has not been well validated in specific high-risk groups such as patients with APOL1-mediated kidney disease and polycystic kidney disease.
- The outcome kidney failure, defined as initiation of chronic dialysis or pre-emptive kidney transplant, relies on local practice.

Why Use

Particularly for individuals with eGFR <60 ml/min/1.73m^2, the KFRE complements the eGFR- and uACR-based KDIGO CKD staging and risk classification system by providing individualized 2- and 5-year kidney failure risk estimates. By providing individualized prognostic information beyond population-based risk classification, it facilitates risk communication, referral timing, kidney replacement therapy education, and dialysis access planning. Used alongside eGFR thresholds, it more accurately identifies patients who would benefit from referral without increasing referral burden.

II. NEXT STEPS

Advice

The KFRE is designed to be used in stable outpatients and can assist with the following:

Nephrology Referral

- Specific thresholds have not been provided, but generally, patients at low risk can be followed in primary care in accordance with international CKD guidelines (Kidney Diseases Improving Global Outcomes, KDIGO), a referral to a nephrologist is recommended in the following cases:
  - If 5-year risk of kidney failure is >3%–5%, or if the absolute eGFR is <30 mL/min/1.73 m^2, or if GFR decline is rapid, if unexplained significant albuminuria and for thorough evaluation of the cause of kidney disease if the cause is unclear.
  - Note: For those meeting the eGFR threshold alone, assessing predicted KFRE risk and prioritizing those at >1% 2-year KFRE may improve identification of patients at higher than low risk of progression most likely to benefit from referral.

Multidisciplinary CKD care

- The KDIGO recommends that patients with 2-year kidney failure risk of ≥10% in addition to meeting the eGFR threshold of <30 mL/min/1.73m^2 be also considered for multidisciplinary CKD care including renal dieticians and pharmacists to delay CKD progression, manage complications of CKD and discuss kidney replacement therapy (KRT) modalities.

Kidney Replacement Therapy Planning

- Patients with 2-year kidney failure risk of ≥40%, should undergo KRT planning such as vascular access planning, and transplant evaluation.

Additional Consideration

- Shared decision making considering the overall prognosis and goals of care of the patient is important.
- The KFRE should not be used for patients in CKD Stages G1 and G2 (eGFR >60 mL/min/1.73 m^2) as the model was not validated in these patients.
- When treating patients outside of North America, clinicians must apply the regional calibration factor to ensure the score reflects local practice patterns.
- The equation assumes eGFR is accurate. In cases where creatinine-based eGFR is inconsistent with the clinical picture (e.g. frail individuals), clinicians should obtain a Cystatin C to improve accuracy.

Management

The first step in management is ensuring accurate diagnosis with estimated GFR and spot urine albumin: creatinine ratio, both necessary for proper CKD evaluation. It is also essential to confirm chronicity and prioritize identifying the cause of CKD (e.g., diabetic nephropathy, obstructive uropathy, IgA nephropathy, polycystic kidney disease), as specific management strategies depend on the underlying etiology. KFRE estimates can complement CKD management to guide timing of nephrology referral, KRT education, vascular access planning, and transplant evaluation (see Next Steps section). Management decision should otherwise follow established comprehensive CKD guidelines (KDIGO) and should broadly include individualized clinical assessment, targeting modifiable risk factors for CKD progression, including glycemic, ASCVD risk and blood pressure control, and promptly initiating CKD-guideline directed medical therapy based on stage, degree of albuminuria and presence of comorbidities such as heart failure and diabetes. Clinicians should refer to the most updated CKD guideline as management recommendations evolve based on new evidence. Note that KFRE is not intended for use for acute GFR changes. Patients may need evaluation by a nephrologist regardless of KFRE risk estimate such as in cases of rapidly kidney function decline with or without unexplained urinary abnormalities.

Critical Actions

- A referral to a nephrologist is critically indicated if the patient's 5-year risk of kidney failure is >3%–5%.
- Patients crossing high-risk threshold of ≥40% kidney failure risk should be prioritized for vascular access planning and transplant referral. This ensures that patients are prepared as well as possible before reaching imminent failure.
- Clinicians must prioritize identifying the primary cause of CKD and aggressively controlling risk factors for progression, such as optimizing glycemic control in patients with diabetes.
- Regardless of the estimated risk, the cause of CKD is not identified and there is rapid progression such as >5ml/min/1.73m^2 per year or >25% decline in a year, it is important to refer to a nephrologist for further investigation; a kidney biopsy may be necessary to identify a reversible cause.

III. EVIDENCE

Evidence Appraisal

The KFRE estimates the risk of kidney failure within 2 and 5 years from a clinic visit. The model was developed and initially validated in large independent Canadian cohorts with CKD stages 3-5 referred to nephrology clinic who were followed from the time of nephrology visit until they started dialysis or underwent kidney transplant. An 8-variable model including age, sex, estimated glomerular filtration rate (eGFR), urine albumin, and serum concentrations of calcium, phosphate, bicarbonate, and albumin had excellent discrimination of the outcome with a C-statistic of 0.92 in the development cohort and 0.84 in the validation cohort. The addition of eGFR and urine albumin alone had the greatest influence on the performance of the model improving the C-statistic from 0.56 based on age and sex alone to 0.89 while the addition of albumin, calcium, phosphorus and bicarbonate provides modest improvement by ~0.03. Traditional risk factors diabetes and hypertension did not improve the model's performance. Kidney failure was defined as the initiation of dialysis or pre-emptive kidney transplantation which although captured through robust methods is practice dependent as it is not standardized. Nonetheless, in a diverse cohort including 721,357 patients with CKD from 31 countries including both general and nephrology clinic patients with a median follow up of 4 years, the original equation performed better than a pooled equation with an overall C statistic 0.90 (95% CI, 0.89-0.92) at 2 years, and 0.88 (95% CI, 0.86-0.90) at 5 years. However, it required adjustment to improve calibration in regions outside North America due to over-estimation. Conversely, in a large, multiethnic urban cohort (n=7,296, 41% Afro-Caribbean) in London, UK, all with type 2 diabetes and CKD stages 3a–5 followed for a median of ~10 years and where kidney failure was defined biochemically as reaching a sustained eGFR <10 mL/min/1.73 m^2 (primary endpoint) or <15 mL/min/1.73 m^2 (secondary endpoint), KFRE tended to under-predict the absolute risk of kidney failure across ethnic groups, suggesting some patients may progress faster than the standard equation estimates. While the model has performed well in a cohort of individuals older than 65 years with advanced CKD (eGFR 10-30 mL/min/1.73m^2), the equation does not factor in the risk of cardiovascular mortality which is important to consider in this population and may lead to overestimation in older adults. This tool may also under-predict risk in certain populations at higher risk of progression. It has been found to have poor calibration for patients with certain CKD etiologies such as polycystic kidney disease, tubulointerstitial disease and unknown etiology. A study including patients followed in nephrology clinics from 34 US centers showed that variability in median year to kidney failure decreased with higher KFRE thresholds. The 4-variable model has been validated in a large cohort with eGFR estimated by the race-free CKD-EPI 2021 and particularly performed well in those with eGFR <45ml/min/1.73m^2. Addition of cardiovascular comorbidities and 2-year eGFR slope did not improve model performance. KFRE could improve prioritization of patients for referral based on individual risk of progression. A VA study of 399,644 adults under primary care, showed that a significant proportion of patients that met laboratory-based indications for nephrology referral such as eGFR <30 mL/min/1.73m^2 had a low 2-year KFRE (1%) and that using KFRE thresholds could better target the ideal population that would benefit from referral limiting significant referral burden. Furthermore, in a Canadian study of 2581 adults with eGFR <20 mL/min/1.73m^2 who chose hemodialysis as modality, use of KFRE-2year >40% as an adjunct to eGFR-based referral for vascular access planning was found to have higher sensitivity for KRT initiation and was associated with significantly lower too-early creation of vascular access compared to eGFR-based referral alone.

Formula

North America

$$\text{Probability} = 1 - 0.9096^{x}$$

Non-North America

$$\text{Probability} = 1 - 0.9245^{x}$$

Where $x = \exp(-0.1992 \times (\text{age}/10 - 7.036) + 0.1602 \times (\text{male} - 0.5642) - 0.4919 \times (\text{eGFR}/5 - 7.222) + 0.3364 \times (\log(\text{ACR}) - 5.137) - 0.3441 \times (\text{albumin} - 3.997) + 0.2604 \times (\text{phosphorous} - 3.916) - 0.07354 \times (\text{bicarbonate} - 25.57) - 0.2228 \times (\text{calcium} - 9.355))$

Facts & Figures

Performance of 4-variable KFRE in various cohorts

Study / Cohort	Cohort Characteristics	Outcome & Follow-up	Discrimination (C-stat/AUC)	Calibration
Tangri *et al.*Meta-analysis (JAMA 2016)	Multinational CKD Prognosis Consortium — 721,357 adults with CKD stages 3-5 from 31 cohorts across >30 countries; diverse age, race, comorbidity	Kidney failure (dialysis/ transplant), 2-yr & 5-yr	2-yr pooled: ~0.90 (95% CI 0.89–0.92); 5-yr pooled: ~0.88 (95% CI 0.86–0.90)	Overall high discrimination; calibration generally good but varied by region and sometimes required *recalibration* outside initial cohorts.
CKD-CAREMEAU cohort (PMC12415514)	France; 3,191 CKD pts (all stages); median age 71; ~60% male; diverse etiologies (vascular ~37%, diabetes ~21%, glomerular ~16%, etc.)	Kidney failure (KRT) within 5 yrs	Discrimination generally ~0.83–0.94 in etiologic subgroups	Calibration varied by CKD cause: good in vascular/diabetic; poorer in polycystic & tubulointerstitial disease.
Ethnically Diverse T2DM CKD Cohort (Goubar *et al.*, PMID 39277182)	UK; 7,296 adults with T2DM & CKD (median eGFR ~48); ~41% African-Caribbean, ~45% Caucasian	ESKD defined as eGFR < 10 or <15 mL/min/ 1.73 m^2^; up to 10.2 yrs	Primary outcome: 2-yr 0.842; 5-yr 0.816; Secondary similar (~0.843 & ~0.801)	Original KFRE under-predicted risk overall and by ethnicity; recalibration substantially improved calibration (ICI & E90 metrics).
KFRE w/ CKD-EPI 2021 across 59 cohorts (Grams *et al.*, JASN 2023, PMID: 36857500)	CKD Prognosis Consortium 59 cohorts; 312,424 CKD pts with eGFR <60	KRT at 2 & 5 yrs	Generally strong discrimination Median 2-yr C-stat: 0.921 (IQR 0.903–0.939); 5-yr C-stat: 0.898 (IQR 0.883–0.919)	Accurate/ calibrated overall using CKD-EPI 2021 eGFR; subgroup miscalibration at eGFR 45-59 (underprediction) & older adults (over-prediction).

KRT, kidney replacement therapy, ICI, Integrated Calibration Index, E90, 90th percentile of the absolute difference between observed and predicted probabilities

Estimates and model performance in the development dataset

Models	Variables	HR	C-statistic
1	Age, per 10 y	0.86	0.56
	Male	1.03	
2	Age, per 10 y	0.75	0.89
	Male	1.46	
	Baseline eGFR, per 5ml/min/1.73m^2	0.54	
3	Age, per 10 y	0.80	0.91
	Male	1.26	
	Baseline eGFR, per 5ml/min/1.73m^2	0.57	
	Log spot urine ACR	1.60	
4	Age, per 10 y	0.80	0.91
	Male	1.27	
	Baseline eGFR, per 5ml/min/1.73m^2	0.58	
	Log spot urine ACR	1.61	
	Diabetes	0.86	
	Hypertension	1.17	
5	Age, per 10 y	0.79	0.92
	Male	1.34	
	Baseline eGFR, per 5ml/min/1.73m^2	0.60	
	Log spot urine ACR	1.55	
	Systolic, per 10 mmHg	1.15	
	Diastolic, per 10 mmHg	1.10	
	Body weight, per 10 kg	0.91	
6	Age, per 10 y	0.82	0.92
	Male	1.16	
	Baseline eGFR, per 5ml/min/1.73m^2	0.61	
	Log spot urine ACR	1.42	
	Serum albumin, per 0.5 g/dL	0.84	
	Serum phos, per 1.0 mg/dL	1.27	
	Serum bicarb, per 1.0mEq/L	0.92	
	Serum calcium, per mg/dL	0.81	
7	Age, per 10 y	0.82	0.92
	Male	1.26	
	Baseline eGFR, per 5ml/min/1.73m^2	0.64	
	Log spot urine ACR	1.37	
	Diabetes	0.88	
	Hypertension	0.89	
	Systolic, per 10 mmHg	1.14	
	Diastolic, per 10 mmHg	1.15	
	Body weight, per 10 kg	0.91	
	Serum albumin, per 0.5 g/dL	0.83	
	Serum phos, per 1.0 mg/dL	1.34	
	Serum bicarb, per 1.0mEq/L	0.93	
	Serum calcium, per mg/dL	0.82	

Literature

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