What is the most reliable score to predict progression of chronic kidney disease to ESRD in older patients with CKD stage 3b or higher (eGFR<45ml/min/1.73m²)?

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European Renal Best Practice Guidelines

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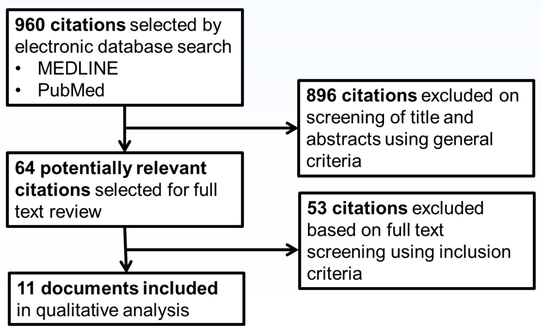
Introduction

The prevalence of CKD increases sharply with age such that almost 50% of people aged over 70 years are affected, but only a minority progress to end-stage kidney disease. It is therefore important to have an accurate method to predict risk of progression in older people so that high risk persons can be identified early to allow adequate time for preparation for possible renal replacement therapy (RRT) whereas those at low risk can be spared unnecessary preparation. We therefore sought to identify the most reliable risk prediction equation for use in older people.

Methods

We conducted a systematic literature search in PubMed and MEDLINE. “Elderly” was defined as older than 65 years; progression of CKD was defined as progression to CKD stage 5 (category G5), a point which would generally prompt initiation of discussion regarding possible RRT in the elderly. The abstracts of all papers were assessed independently by two assessors. Differences were resolved by discussion. From the initial search papers were identified for detailed review and data extraction.

Results



The literature search identified 960 papers, 64 were selected for detailed review and 11 for data extraction (Table). Two were excluded because they included participants without CKD (5,6). After data extraction, we identified 3 prospective (1,2,4) and 6 retrospective (3, 7-11) cohort studies that aimed to identify risk factors and/or develop a risk prediction score for progression to ESKD in predominantly older people. All of the prospective studies and two retrospective studies (7,9) were excluded from further consideration because they did not attempt to develop a risk prediction score. A further retrospective study was excluded due to significant selection bias and missing data (8). A retrospective study that included data from predominantly male patients at a Veterans Administration (VA) Medical Centre performed well but did not include a measure of proteinuria and has not been validated in general populations (3). The Kidney Failure Risk Equation (KFRE) was developed in Canadian adults who were referred to Nephrologists with eGFR 10-59ml/min/1.73m^2. The 8-variable KFRE achieved excellent discrimination in development (C statistic=0.917) and validation cohorts (C statistic=0.841) and a 4-variable KFRE performed almost as well (10). 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. The 4-variable KFRE achieved excellent discrimination with a pooled C statistic of 0.90 at 2 years and 0.88 at 5 years. Discrimination was similar in subgroups aged ≥65 years versus younger for both the 4- and 8-variable KFRE. To improve calibration in non-American populations, a correction factor was applied. Further subgroup analysis confirmed good discrimination in people aged >65 years with eGFR<45ml/min/1.73m^2 (11).

Study	Year Location	Design	Inclusion criteria Exclusion criteria	Patients' characteristics	Comparator Groups	Outcome(s)	Results	Quality of evidence
1. Dalrymple LS J Gen Int Med 2011; 26:379-85	2010 USA	Prospective	Inclusion: • age ≥65y • eGFR<60 Exclusion: • institutionalized • intention to move within 3y • wheelchair use within home • hospice care • current chemotherapy or radiation for cancer.	Community dwelling older people from the CHS: • mean age75years • mean eGFR 51	eGFR <60-45 (n=985) eGFR<45 (n=283)	ESKD (need for RRT) All cause mortality CV mortality	Event rates/100 person years: eGFR <60-45: ESKD 0.3 (0.2, 0.4) Mortality 6.1 (5.6, 6.6) CV mortality 2.6 (2.3, 3.0) eGFR<45: ESKD 1.8 (1.2, 2.4) Mortality 10.3 (8.8, 11.7) CV mortality 4.8 (3.8, 5.8) Independent risk factors for ESKD: male, African-American, BMI≥25, lower eGFR Independent risk factors for death: older age, male, BMI<18.5, hypertension, diabetes, cardiovascular disease, heart failure, former and current tobacco use	Good quality study but no measure of proteinuria available. No risk score. Sub-group with eGFR<45 small. Primary purpose of study was to study epidemiology of cardiovascular disease.
2. De Nicola L Kidney Int. 2012; 82:482-8	2012 Italy	Prospective	Inclusion: • eGFR<60 • Nephrology clinic attendance >1y Exclusion: • AKI within 6m	Consecutive patients attending 25 Nephrology clinics • mean age 67 years • mean eGFR 31	Age<65y (n=481) Age65-75 (n=410) Age>75y (n=357)	-ESKD (start of RRT) -Death without ESKD	Overall risk of ESKD exceeded risk of death without ESKD. Event rates in 3 age groups: ESKD: 9.0 (95% CI 7.8–10.4), 7.3 (95% CI 6.1–8.8), 7.9 (95% CI 6.4–9.8) Death without ESKD: 1.2 (95% CI 0.8–1.7), 5.2 (95% CI 4.2–6.5), 12.6 (95% CI 10.7–14.9) Independent risk factors for ESKD: Age, male, lower BMI, lower Hb, higher phosphate , interactions between age and proteinuria, age and CVD Independent risk factors for death without ESKD: Age, CVD, ESKD, higher uric acid, lower Hb. Interaction betwen diabetes and age.	Good quality study Highly selected study poplation All Caucasian No risk score
3. Drawz PE J Am Geriatr Soc 2013; 61:762-8	2013 USA (VA)	Retrospective	Inclusion: • age≥65y • eGFR<30 Exclusion • Dialysis • Kidney transplant	Predominantly elderly male patients from two VA hospitals. Developmental cohort: • mean age 77.5y; 95% male; 12% Black; mean GFR 25. Validation cohort: • mean age 78.1y; 98% male 8% Black; mean GFR 25	Developmental cohort: n=1866. Validation cohort: n=819.	ESKD within 1 year of index GFR ESKD=GFR<15 or RRT	Final predictive model included: eGFR, age, CHF, SBP (average of last 5), most recent potassium and albumin, and interactions between age and eGFR and eGFR and CHF. C-statistic=0.854. C-statistic in validation cohort=0.823. C-statistic for Tangri risk score in both cohorts=0.780	Predominantly male study population. GFR range lower than in PICO. Retrospective study. Validation cohort similar to developmental cohort, therefore external validation required.
4. Faller B BMC Nephrol 2013; 14:103	2013 France	Prospective multicentre	Inclusion: • age≥80y • creatinine >170µmol/L (males) or >150µmol/L (females) • new referral to nephrology or <9m follow-up Exclusion: • dialysis initiation planned <3 m	• mean age 85y • mean GFR=24	n=155	Initiation of dialysis or death at 2 years	Cox proportional hazards model: only eGFR<23 predicted ESKD. Fine and Gray analysis: eGFR<23 and DBP predicted ESKD	Poor quality study: Small study population. 25 participants lost to follow-up or no longer followed up. No risk score
5. Halbesma N Clin J Am Soc Nephrol 2011; 6:1731-8	2011 Nether-lands	Prospective	PREVEND study Inclusion: • 2 or 3 follow-up GFRs Exclusion: • eGFR<45 • known CKD • no follow-up GFR	Non-progressors: • mean age 49y • mean GFR=81.4 Progressors: • mean age 61y • mean GFR=68.9	n=6809 Non-progressors (n=6537) Progressors (n=272)	Progressive CKD: top 20% of GFR decline plus eGFR<60 during follow-up	Final model included eGFR, age, albuminuria, systolic BP, C-reactive protein, and known hypertension. AUROC curve=0.84 (or 0.83 for clinically applicable score)	Good quality study but inclusion criteria and outcome do not match the PICO. No external validation.
6. Hemmelgarn B QJM 2007; 100:87-92	2007 Canada	Retrospective	Inclusion: • age ≥66y • ≥1 out-patient serum creatinine Exclusion: • Dialysis • >12 out-patient serum creatinine in 6 months • eGFR ≥90.	• mean age 76.1y in both cohorts • GFR 60-98 in 64.5% • GFR 30-59 in 31.1% • GFR<30 in 4.1%	Derivation (n=6789) Validation (n=3395)	Rapid progression of CKD defined as >25% decline in GFR over 2 years	Final model included: age >75 years, cardiac disease, diabetes mellitus, gout, use of anti-emetic medications. C-statistic=0.59 for both derivation and validation cohort	Poor quality: Inclusion criteria and outcome do not match the PICO. No external validation. Data limited to demographic data, medication and serum creatinine. C-statistic low.
7. Johnson ES Am J Kidney Dis 2007; 50:559-65	2007 USA	Retrospective	Inclusion: • eGFR<60 on 2 occasions ≥90 days apart • membership of KPNW ≥1y • prescription drug coverage with KPNW for ≥1y • age ≥20y Exclusion: • receiving RRT	• mean age 74y	n=6541	Time to RRT Time to death Time to RRT or death.	Final model included age, sex, eGFR, diabetes, hypertension, and anemia for all outcomes. C-statistic for RRT=0.84; C-statistic for death=0.70; C-statistic for both=0.71 Subgroup analysis including only participants ≥65y gave c-statistic=0.89 for RRT	Poor quality: Inclusion criteria do not match the PICO. Retrospective therefore data not collected by protocol. Proteinuria not included due to missing data. Data on ethnicity not available. No risk score.
8. Johnson ES Am J Kidney Dis. 2008; 52: 653-60	2008 USA	Retrospective	Inclusion: • eGFR 59-15 on 2 occasions ≥90 days apart; membership of KPNW ≥1y • prescription drug coverage with KPNW for ≥1y • age 30-89y Exclusion: • receiving RRT	• mean age 73y • GFR 45-59 in 65% • GFR 44-30 in 27% • GFR 29-15 in 8%	n=9782	Time to RRT	Final model included age, sex, eGFR, diabetes, anemia, and hypertension. C-statistic=0.89	Poor quality: Inclusion criteria do not match the PICO. Retrospective therefore data not collected by protocol. Proteinuria not included due to missing data. Data on ethnicity not available.
9. Obi Y Clin J Am Soc Nephrol 2010; 5:1558-65	2010 Japan	Retrospective	Inclusion: • eGFR<60 • referred to nephrology Exclusion: • Malignancy • previous RRT • refused RRT • Immune suppressants for renal disease	• median age 67y • GFR 30-59 in 45% • GFR 15-29 in 31.2% • GFR<15% in 27.8%	n=461	Initiation of RRT Death	Older age independently associated with increased risk of death. Younger age and overt proteinuria independently associated with RRT. Among patients >65y with CKD stage 3 and without proteinuria, none required RRT.	Poor quality: Inclusion criteria do not match PICO. Retrospective. No risk score. Small number of participants.
10. Tangri N JAMA 2011; 305:1553-9	2011 Canada	Retrospective	Inclusion: • eGFR 59-10 • referred to nephrologist	Development cohort: • mean age 70y • mean eGFR 36. Validation cohort: • mean age 69y • mean eGFR 31.	Development (n=3449) Validation (n=4942)	Initiation of RRT	Kidney Failure Risk Equation (KFRE) Best model included: age, sex, eGFR, albuminuria, serum calcium, serum phosphate, serum bicarbonate, and serum albumin. C statistic=0.917 in development cohort and 0.841 in validation cohort.	Good quality study but retrospective. Inclusion criteria did not match PICO. Requires further external validation.
11. Tangri N JAMA 2016; 315:164-74	2016 Multi-centre	Meta-analysis	Inclusion: • CKD stage 3-5 (eGFR<60) Exclusion: • ESKD	• mean age 74 years • mean eGFR 46	N=721,357 31 cohorts	Initiation of RRT	Kidney Failure Risk Equation (KFRE) 4-variable model included age, sex, eGFR, albuminuria. 8-variable model included: age, sex, eGFR, albuminuria, serum calcium, serum phosphate, serum bicarbonate, and serum albumin. C-statistic for 4- variable model for risk at 2- and 5-years 0.90 and 0.88, respectively. C-statistic for 8-variable model for risk at 2- and 5-years 0.89 and 0.86, respectively. Discrimination similar in subgroup ≥65 years Calibration factor required to improve performance in European populations. Further subgroup analysis in people ≥65 y and eGFR<30 showed C-statistic of 0.87 and 0.86 for 4-variable KFRE and 0.88 and 0.86 for 8 variable KFRE at 2 and 5 years, respectively.	Good quality study. Very large validation cohort. Subgroup analysis with inclusion criteria that exactly match the PICO.

Conclusion

We recommend that the 4-variable Kidney Failure Risk Equation (KFRE) predicts the risk of progression of CKD to ESRD in older patients at stage 3b or higher (GFR<45ml/min/1.73m^2), sufficiently well to be a useful aid to shared decision making (1B).

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