Validation of the Kidney Failure Risk Equation in a Large Portuguese Cohort: Analysis of Diabetic and Heart Failure Subgroups

Ana Rita Lopes de Almeida[1], Mafalda Santos Filipe[1], Beatriz Donato[1], Adriana Fernandes[1], Sónia Silva[1], Edgar Almeida[1], Luís Pedro Falcão[2], Mário Raimundo[1]*

1. Nephrology Department, Unidade Local de Saúde de Loures / Odivelas, Loures, Portugal
2. Nephrology Department, Unidade Local de Saúde de Braga, Braga, Portugal

https://doi.org/10.71749/pkj.140

Abstract

Introduction: The Kidney Failure Risk Equation (KFRE) is a validated tool for predicting kidney replacement therapy (KRT) initiation. However, its performance in Portuguese populations and specific subgroups, such as those with diabetic kidney disease (DKD) and heart failure (HF), requires further validation.

We aimed to validate the 4-variable KFRE at 2 and 5 years in a Portuguese chronic kidney disease (CKD) cohort and assess its performance in DKD and HF subgroups.

Methods: Retrospective cohort study of 1741 consultations from 1728 patients (CKD stages 3–5) followed between 2012 and 2019. Discriminatory power was evaluated using the area under the receiver operating characteristic curve (AuROC).

Results: The cohort had a median age of 73.9 years (IQR 13.9) and a median eGFR of 34 mL/min/1.73m². During a median follow-up of 25.9 months in the 2-year cohort (N=1741) and 38.2 months in the 5-year cohort (N=806), 167 (9.6%) and 242 (30.0%) patients initiated KRT, respectively, and 331 (19.0%) died. The KFRE showed good discrimination, with an AuROC of 0.914 (95% CI: 0.884–0.944) at 2 years and 0.914 (95% CI: 0.888–0.940) at 5 years. In the DKD subgroup, discrimination was higher at 5 years (AuROC 0.942) than at 2 years (0.918). In the HF subgroup, discrimination remained accurate, although slightly lower at 2 years (AuROC 0.873) than at 5 years (0.906). Discrimination remained high after excluding stage 5 CKD. Limitations include the retrospective design and high competing mortality.

Conclusion: The 4-variable KFRE showed good discrimination for predicting KRT in Portuguese CKD patients over both 2- and 5-year time horizons. Its adequate discrimination in DKD and HF subgroups supports its clinical utility for risk stratification and transition of care.

Keywords: Diabetic Nephropathies; Heart Failure; Kidney Failure, Chronic; Renal Insufficiency, Chronic; Models, Theoretical; Risk Assessment

INTRODUCTION

Chronic kidney disease (CKD) represents a major global health burden, with progression to end-stage kidney disease leading to substantial morbidity, mortality, and healthcare expenditure. Accurate risk stratification is essential to identify patients most likely to benefit from nephrology specialist care and to progress to kidney failure requiring kidney replacement therapy (KRT), allowing for resource and clinical management optimization.[1–3]

The Kidney Failure Risk Equation (KFRE) has emerged as one of the most widely validated prognostic tools for predicting the 2- and 5-year risk of kidney failure.[4] Developed using large cohorts and based on four readily available clinical variables—age, sex, estimated glomerular filtration rate (eGFR), and urine albumin-to-creatinine ratio (ACR) —the 4-variable KFRE has been validated internationally across multiple populations.[5–16] This tool enables individualized estimation of kidney failure risk, allowing referral and management in secondary care to be tailored according to projected risk rather than determined solely by a specific eGFR threshold.[17]

To our knowledge, the validation of the KFRE in the Portuguese population has been limited to the 2-year formula.[18] Additionally, its performance in clinically important

Received: 10/03/2026 **Accepted:** 30/10/2026 **Published Online:** 10/11/2026 **Published:** -

* **Corresponding Author:** Ana Rita Lopes de Almeida | ritalmeida95@gmail.com | Nephrology Department, Unidade Local de Saúde de Loures / Odivelas, Av. Carlos Teixeira 3, 2674-514 Loures, Portugal

© PKJ 2026. Re-use permitted under CC BY-NC 4.0. (https://creativecommons.org/licenses/by/4.0/)

subgroups—such as individuals with diabetic kidney disease (DKD) and heart failure (HF)—remains underexplored.[19,20] These groups often present distinctive progression patterns: diabetic patients typically exhibit higher albuminuria, potentially enhancing the predictive performance of KFRE, whereas in heart failure patients the initiation of dialysis may be influenced not only by eGFR decline but also by volume overload and symptom-driven considerations.

The present study aimed to validate both the 2-year and 5-year 4-variable KFRE in the largest real-world CKD cohort in Portugal to date. To our knowledge, this is the first Portuguese study validating the 5-year KFRE, currently recommended by international guidelines as a referral criterion.[21] The study also aims to assess the formula discriminative performance in diabetic and heart-failure subpopulations.

METHODS

Design and Population

We conducted a retrospective cohort study including adult patients with CKD stages 3 to 5 who were followed in a Nephrology outpatient clinic, between January 2012 and December 2019, at a secondary hospital in the Lisbon region. Patients were eligible for inclusion if they had a first nephrology outpatient consultation between 2012 and 2019, were classified as CKD stages 3–5 (eGFR <60 mL/min/1.73 m²) and had complete baseline data (including eGFR and urine albumin-to-creatinine ratio) to allow KFRE calculation. Patients were excluded if they had CKD stages 1–2, lacked a baseline urine albumin-to-creatinine ratio measurement, or had insufficient follow-up time to ascertain the progression outcome (death, kidney replacement therapy initiation, or censoring point). Urine ACR was measured at each consultation, when available, and expressed in mg/g. For the KFRE calculation, we used the urine ACR measured closest to the date of the first nephrology appointment, with a maximum interval of three months.

Of 2992 patients screened, 1264 were excluded (780 due to CKD stage 1–2; 205 due to missing baseline urine albumin-to-creatinine ratio; and 279 due to insufficient follow-up for the progression analysis), yielding a final analytic cohort of 1741 consultations from 1728 unique patients. This difference reflects 13 patients with two records, mainly because they were re-referred after a period of more than one year without follow-up; each re-referral was considered a new first consultation. The study protocol was approved by the institutional scientific and ethics committees. Due to the study's observational and retrospective design, the need for written informed consent collection was waived.

Data Collection

Baseline demographic and clinical data were collected from electronic medical records at the time of the first appointment during the study period, including age, gender, race, comorbidities, CKD etiology, medication, echocardiographic data and laboratory results. The outcomes of KRT initiation (hemodialysis, peritoneal dialysis or transplantation) and death were recorded. Patients were followed for a maximum period of 5 years or until initiation of KRT, death or loss to follow-up, whichever occurred first.

Definitions

CKD staging followed KDIGO guidelines and was based on albuminuria and eGFR, calculated using the 2009 CKD-EPI equation.[21,22] A diagnosis of DKD was considered whenever there was a kidney biopsy confirming it or the attending physician(s) registered it as the most likely CKD etiology. Renal biopsy was performed only in atypical presentations; the proportion of biopsy-confirmed versus clinically-diagnosed DKD cases, and the adjudication rule for patients with mixed etiologies, could not be reconstructed retrospectively.

HF diagnosis was established on clinical and echocardiographic grounds, whenever the attending physician(s) listed that diagnosis or there was evidence of abnormal left ventricular ejection fraction.

Statistical Analysis

Categorical variables are presented as frequencies and percentages and continuous variables as mean ± standard deviation if normally distributed or as median [interquartile range (IQR)] if skewed distributed. For univariate comparisons between groups the t-student test or the Mann–Whitney U-test were employed, as appropriate according to distribution. Categorical variables were compared between groups with the chi-squared test.

Risk prediction was performed using the KFRE non–North American 4-variable models at 2 and 5 years, including age, sex, eGFR, and urine albumin-to-creatinine ratio. Subgroup analyses were performed for patients with DKD and HF. The predictive performance of the KFRE (for the entire cohort and for the DKD and HF subgroups) was evaluated using the area under the receiver operating characteristic curve (AuROC). The Youden index was calculated to define the optimal KFRE cut-off for predicting KRT initiation. Additionally, as an exploratory analysis that was not part of the external validation of the KFRE, multivariable Cox proportional hazards regression was used to study other predictors of KRT initiation in our cohort.

Exploratory multivariable Cox models were constructed including the KFRE-predicted risk (substituted for eGFR and urine ACR to avoid collinearity, as these are components of the KFRE) together with all other baseline variables that were statistically significant in the univariable analysis (weight, Black race, smoking, BMI >25 kg/m², dyslipidemia and atrial fibrillation), together with hypertension, which was retained despite not reaching univariable

significance (p=0.28) because of its clinical relevance to CKD progression. Age, although significant univariably, was not entered as a separate covariate, since it is a direct component of the KFRE (along with eGFR and urine ACR) and would introduce the same collinearity. Because weight and BMI>25 were collinear (r=0.60), only BMI>25 was retained in the final model. The proportional-hazards assumption was assessed for all Cox models using Schoenfeld residuals. To account for the competing risk of death, we additionally compared the naive cumulative incidence of KRT (1 minus Kaplan-Meier, treating death as censoring) with the Aalen-Johansen cumulative incidence function (CIF), and fitted cause-specific Cox models for KRT (censoring death) and for death (censoring KRT), using the full observed follow-up. Calibration was assessed by comparing, within deciles of KFRE-predicted risk, the mean predicted risk with the observed CIF at the corresponding horizon (24 or 60 months). Hazard ratios for the KFRE are reported per 1 percentage-point absolute increase in the KFRE-predicted probability of kidney failure. A two-tailed p-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM® SPSS® Statistics 22, complemented by Python.

RESULTS

Baseline Characteristics and Major Outcomes

A total of 1741 consultations from 1728 patients were included (Table 1); 1419 had data to calculate the KFRE and were included in the 2-year analysis, and 658 in the 5-year analysis (Table 2).

Table 1. Univariable analysis comparing the groups that started and who did not start kidney replacement therapy (KRT) at 2 years.

Variable	All patients (N= 1741)	Did not start KRT (N = 1574)	Started KRT (N = 167)	*p*
Age (median, IQR)	74 (14)	74.3 (13.3)	67 (22.4)	0.001
Weight (median, IQR)	71.8 (23.4)	74.9 (19.1)	70.3 (19.9)	0.004
eGFR (median, IQR)	34.0 (20.4)	35.4 (18.8)	13.9 (10.4)	< 0.001
Urine ACR, mg/g (median, IQR)	135.1 (613.3)	68.0 (390.3)	1131.9 (2404.1)	< 0.001
Black race (N, %)	83 (4.8)	61 (3.9)	22 (13.3)	< 0.001[a]
Male (N, %)	963 (55.3)	864 (54.9)	99 (59.3)	0.278
DKD (N, %)	550 (31.6)	489 (31.1)	61 (36.5)	0.149
Smoker (N, %)	203 (11.7)	169 (12.9)	34 (25)	< 0.001[a]
BMI > 25	1084 (62.3)	994 (66.8)	90 (55.2)	0.004[a]
Diabetes	846 (48.6)	766 (48.7)	80 (47.9)	0.851
Hypertension	1540 (88.5)	1399 (88.9)	141 (84.4)	0.087[a]
Dyslipidemia	833 (47.8)	775 (49.2)	58 (34.7)	< 0.001[a]
Heart failure	502 (28.8)	445 (28.3)	57 (34.1)	0.116
VPD	79 (4.5)	70 (4.5)	9 (5.4)	0.579
COPD	118 (6.8)	106 (6.7)	12 (7.2)	0.827
Malignancy	161 (9.2)	150 (9.5)	11 (6.6)	0.211
Dementia	22 (1.3)	21 (1.3)	1 (0.6)	0.418
Atrial fibrillation	215 (12.3)	205 (13.0)	10 (6.0)	0.009[a]

KRT: kidney replacement therapy; eGFR: estimated glomerular filtration rate; DKD: diabetic kidney disease; BMI: body mass index; ACR: albumin-to-creatinine ratio; VPD: vascular peripheral disease; COPD: chronic obstructive pulmonary disease.

[a] Variables included in the multivariable analysis. eGFR, urine ACR, and age were replaced by (or subsumed within) the KFRE-predicted risk in the multivariable model to avoid collinearity, as all three are components of the KFRE (see Supplementary Table S9); weight was excluded owing to collinearity with BMI>25. Hypertension was not significant univariably but was retained in the multivariable model based on its clinical relevance.

Table 2. Summary of area under the receiver operating characteristic curve (AuROC) analysis for overall and subgroup populations

Group	N (2y / 5y)	2-Year AuROC (95% CI)	5-Year AuROC (95% CI)
Overall	1,419 / 658	0.914 (0.884–0.944)	0.914 (0.888–0.940)
DKD	462 / 218	0.918 (0.868–0.968)	0.942 (0.907–0.977)
Non-DKD	957 / 440	0.912 (0.874–0.950)	0.898 (0.863–0.934)
HF	405 / 174	0.873 (0.802–0.944)	0.906 (0.852–0.959)
Non-HF	1,014 / 484	0.932 (0.903–0.960)	0.917 (0.887–0.946)

DKD: diabetic kidney disease; HF: heart failure; AuROC: area under the receiver operating characteristic; 2y curve: 2 year Kidney Failure Risk Equation Formula; 5y: 5 year Kidney Failure Risk Equation Formula; CI: confidence interval.

Median age was 73.9 years (IQR 13.9), 963 (55.3%) were male, and 1632 (93.8%) were caucasian. Regarding comorbidities, 88.5% of patients had hypertension, 846 (48.6%) had diabetes, and 28.8% had heart failure. The full breakdown of CKD etiologies was: DKD (31.6%), ischemic/hypertensive nephrosclerosis (30.5%), other/unknown (12.9%), chronic glomerulonephritis (8.0%), uropathy (5.9%), no indication/unspecified (4.9%), nephrolithiasis (4.0%), polycystic kidney disease (2.0%), and other (0.3%). At baseline, the median eGFR was 34.0 mL/min/1.73 m² (IQR 20.4), and median urine ACR was 135.1 mg/g (IQR 613.3). Baseline medication use included statins (31.4%), renin-angiotensin-aldosterone system inhibitors (61.7%), loop diuretics (43.1%), thiazides (18.4%), and potassium-sparing diuretics (2.2%). The distribution of CKD eGFR stages at baseline was: 399 (22.9%) in stage 3A, 645 (37.0%) in stage 3B, 546 (31.4%) in stage 4, and 151 (8.7%) in stage 5.

Median follow-up was 25.9 months in the 2-year cohort (N=1741) and 38.2 months in the 5-year cohort (N=806). Overall, 331 patients (19.0%) died; 167 (9.6%) progressed to KRT within 2 years, and 242 (30.0%) within 5 years (of the 806 patients eligible for the 5-year analysis). Patients who started KRT at two years were younger, had lower eGFR and higher urine ACR at baseline, had lower weight and body mass index, were more likely to be black and to be smokers and less likely to have dyslipidemia or atrial fibrillation.

KFRE VALIDATION

2-Year 4-Variable KFRE

The 4-variable non–North American KFRE showed good discriminative ability in the overall cohort (Fig. 1A).

In the univariable Cox regression model, considering KFRE a continuous variable, each 1-unit increase in KFRE was associated with a 6.2% increased risk of starting KRT (hazard ratio [HR] 1.062; 95% confidence interval [CI] 1.056–1.068; $p<0.001$). The best cut-off value for predicting KRT initiation was 7.9. When KFRE was analyzed in univariable Cox regression analysis as a categorical variable, patients above the cut-off value had a 30-fold higher risk of initiating KRT (HR 30.108; 95% CI 17.726–51.138; $p<0.001$), as presented in Table 3.

Table 3. Univariable analysis of KFRE performance for kidney replacement therapy (KRT) initiation.

Variable	2-Year KRT initiation				5-Year KRT initiation			
	HR	CI	p-value	Youden Index	HR	CI	*p*-value	Youden index
KFRE (continuous)	1.062	1.056–1.068	< 0.001	-	1.045	1.040–1.049	< 0.001	-
KFRE (above YI cut-off)	30.1	17.73–51.14	< 0.001	7.86	19.1	12.69–28.65	< 0.001	18.21

KFRE, Kidney Failure Risk Equation; KRT, kidney replacement therapy; HR, hazard ratio; YI, Youden Index; CI, confidence interval.

When considering only patients in CKD stages 3 and 4 (excluding the 151 patients who were already in stage 5 at baseline), the model maintained an adequate discriminative ability, with an AuROC of 0.865 (95% CI 0.81–0.91, $p<0.001$), as presented in Fig. 1B.

In subgroup analysis by DKD status, the 2-year KFRE showed similar predictive performance for patients with (N = 462) and without DKD (N = 957), with AuROC of 0.918 (95% CI 0.868–0.968) and 0.912 (95% CI 0.874–0.950), respectively (Fig. 1C). Excluding patients with baseline CKD stage 5, results were consistent. As a sensitivity analysis, we redefined the diabetic subgroup more broadly as any patient with diabetes, irrespective of coded CKD etiology (N=846, 48.6% of the cohort). Discrimination remained high under this broader definition, though modestly lower than with the etiology-based definition (2-year AuROC 0.900, N=698; 5-year AuROC 0.917, N=318).

Regarding HF, the 2-year KFRE revealed a lower (although still high) predictive ability for those with HF (N = 405) compared with those without HF (N = 1014) - AuROC 0.873 (95% CI 0.802–0.944) *vs* 0.932 (95% CI 0.903–0.960), respectively (Fig. 1D). When CKD stage 5 patients were excluded (N=86), the 2-year AuROC was 0.819 (95% CI 0.714–0.924) for HF patients *vs* 0.889 (95% CI 0.838–0.939) in non-HF. Left ventricular ejection fraction was documented in 342 of 502 HF patients (68.1%): 57 (16.7%) had HFrEF (LVEF<40%), 57 (16.7%) had HFmrEF (LVEF 40–49%), and 228 (66.7%) had HFpEF (LVEF≥50%). Discrimination was numerically lower in HFrEF than HFpEF at both horizons (2-year AuROC 0.767 *vs* 0.872; 5-year AuROC 0.870 *vs* 0.938), although the small number of HFrEF patients with documented ejection fraction (n=45 at 2 years, 7 events) limits the precision of this estimate. Of the 502 HF patients, 189 (10.9% of the overall cohort) also had DKD; conversely, of the 313 HF patients without a DKD etiology code, 112 (35.8%) were nonetheless diabetic under the broader definition.

AuROC values for each subgroup are summarized in Table 2.

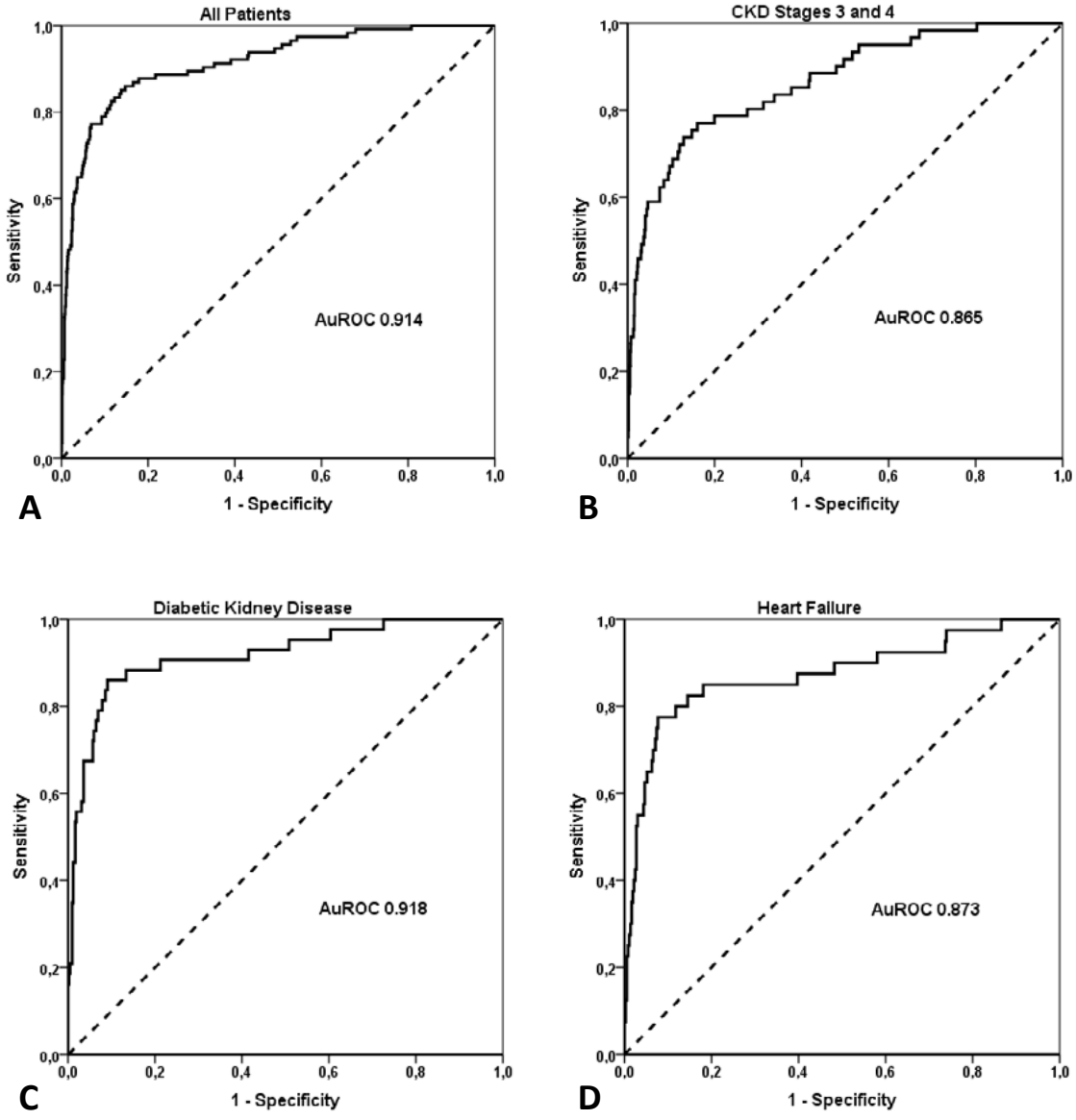


Figure 1. Two-year Kidney Failure Risk Equation receiver operating characteristic curve for all patients (CKD stages 3 to 5) (A), patients with CKD stages 3 and 4 (B), patients with diabetic kidney disease (C) and patients with heart failure (D).

5-Year 4-Variable KFRE

The 4-variable non–North American KFRE for 5 years showed good discriminative ability in the overall cohort (AuROC 0.914, 95% CI 0.888–0.940, $p<0.001$) as shown in Fig. 2A. When considering only patients in CKD stages 3 or 4 (excluding the 114 patients who were already in stage 5 at baseline), the model maintained a similar discriminative ability, with an AuROC of 0.883 (95% CI 0.847–0.918; $p<0.001$), as presented in Fig. 2B.

In the univariable Cox regression model, with KFRE as a continuous variable, each 1-unit increase in KFRE was associated with a 4.5% increased risk of starting KRT (HR 1.045, 95% CI 1.040–1.049; $p<0.001$, Table 3). The best cut-off value for predicting KRT initiation was 18.2. When KFRE was analyzed in univariable Cox regression analysis as a categorical variable, patients above the cut-off value had a 19-fold higher risk of initiating KRT (HR 19.069; 95% CI 12.690–28.654; $p<0.001$).

At 5 years, the predictive ability was slightly higher in DKD patients (AuROC 0.942, 95% CI 0.907–0.977) compared with non-DKD patients (AuROC 0.898, 95% CI 0.863–0.934), though both remained adequate (Fig. 2C).

Regarding the presence of HF, at 5 years the predictive performance was similar between HF and non-HF groups - AuROC 0.906 (95% CI 0.852–0.959) *vs* 0.917 (95% CI 0.887–0.946), respectively (Fig. 2D). When CKD stage 5 patients were excluded, the AuROC was 0.883 (95% CI 0.815–0.951) in HF and 0.880 (95% CI 0.838–0.922) in non-HF, indicating minimal differences.

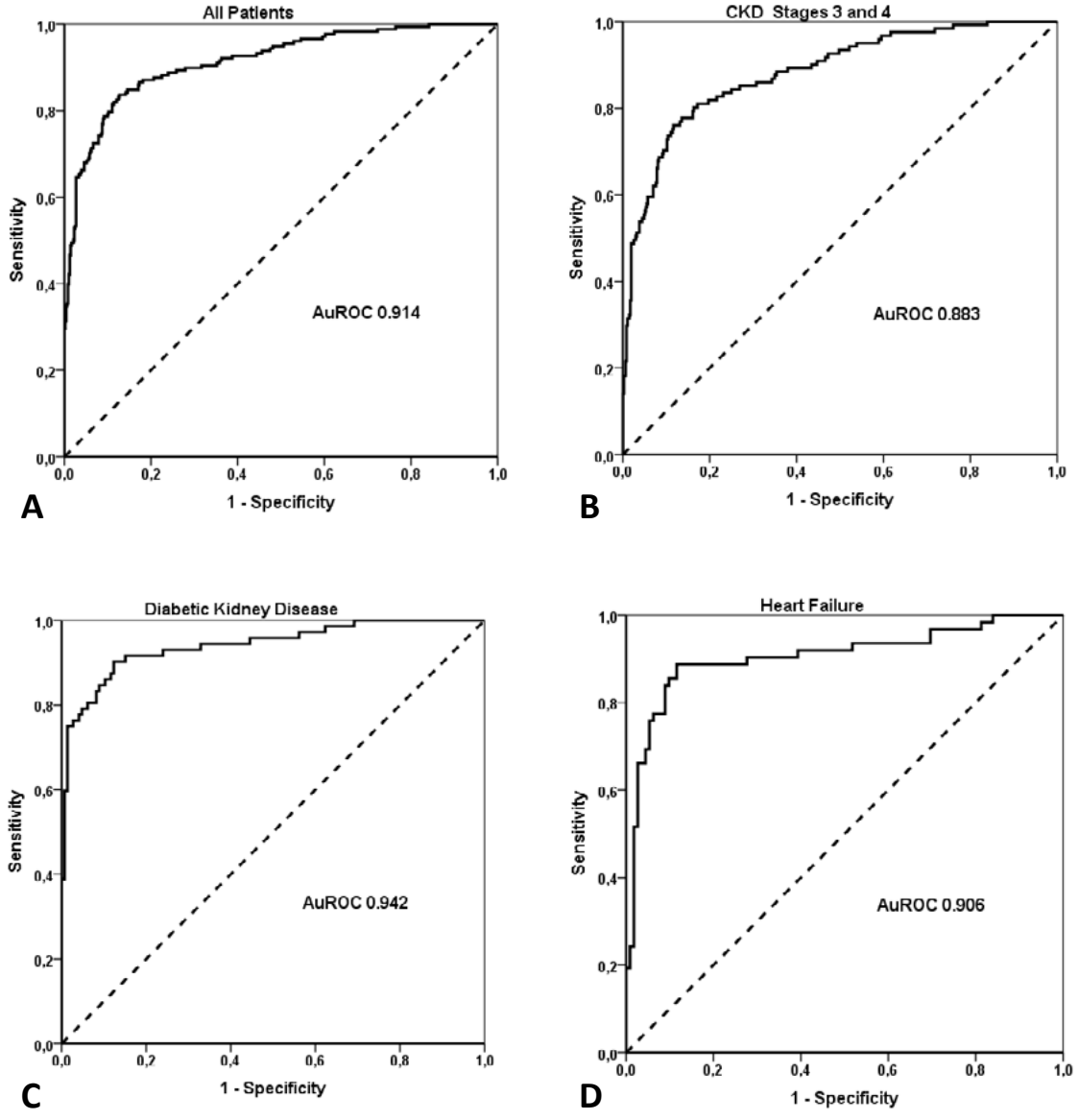


Figure 2. Five-year Kidney Failure Risk Equation receiver operating characteristic curve for all patients (CKD stages 3 to 5) (A), patients with CKD stages 3 and 4 (B), patients with diabetic kidney disease (C) and patients with heart failure (D).

Exploratory Multivariable Cox Regression

In the exploratory multivariable Cox model, which included the KFRE-predicted risk, Black race, smoking, BMI >25 kg/m², dyslipidemia, atrial fibrillation and hypertension, the KFRE-predicted risk remained associated with KRT initiation at 2 years (HR 1.058; 95% CI 1.050–1.066; $p<0.001$) and 5 years (HR 1.039; 95% CI 1.034–1.044; $p<0.001$). None of the other covariates were independently associated with KRT initiation at either horizon (Supplementary Table S9). The proportional-hazards assumption was satisfied for both models (Schoenfeld residuals, $p>0.05$). As this complete-case analysis (N=1060 at 2 years; N=439 at 5 years) was exploratory, these associations should be interpreted with caution.

Competing-Risk Analysis

Using the full observed follow-up, the naive cumulative incidence of KRT (treating death as censoring) modestly overestimated the true Aalen-Johansen cumulative incidence function (CIF) at both 2 years (4.84% *vs* 4.77%) and 5 years (8.65% *vs* 8.39%). In cause-specific Cox models, the KFRE remained a significant predictor of KRT after accounting for the competing risk of death (2-year risk: HR 1.056, 95% CI 1.050–1.061; 5-year risk: HR 1.044, 95% CI 1.040–1.048; both $p<0.001$), and was also independently associated with all-cause mortality (2-year risk: HR 1.016, 95% CI 1.006–1.026, $p=0.001$; 5-year risk: HR 1.009, 95% CI 1.004–1.015, $p<0.001$), presenting death as a correlated competing risk in this population.

Calibration

Calibration by decile of KFRE-predicted risk showed reasonable agreement between predicted risk and observed CIF in the low-to-intermediate deciles, but overestimation in the highest decile (2-year: predicted 45.5% *vs* observed 32.7%; 5-year: predicted 84.7% *vs* observed 53.3%).

DISCUSSION

In this large real-world Portuguese cohort, we validated both the 2-year and 5-year versions of the 4-variable KFRE and assessed their performance in clinically relevant subgroups, including patients with diabetic kidney disease and those with heart failure. To our knowledge, this was the largest study to do so in the Portuguese population and the first one to validate the 5-year KFRE.

Overall, the KFRE presented a good discriminative ability in predicting KRT risk, aligned with previous international validations conducted in diverse CKD populations.[5,6,8,10,13–15,18,23–25] In our study, the 4-variable KFRE achieved an AuROC of 0.914 for both 2-year and 5-year predictions, with similar discrimination at both horizons. These values are higher than those of the European multicenter validation of the 4-variable formula by Ramspek *et al*,[8] which reported C-statistics between 0.78 and 0.84, including a total of 267 479 patients for this analysis. Similarly, our findings exceed the pooled C-statistic of 0.89 reported in the multinational meta-analysis by Tangri *et al*[9] for non-North American cohorts. The consistent discrimination ability across both time horizons in our Portuguese population suggests that the KFRE can adequately rank patients by risk in our clinical reality.

An important methodological consideration of the present study is the analysis excluding patients with stage 5 CKD. The incorporation of individuals with very low eGFR may artificially inflate the predictive performance of risk equations, as these patients are inherently at a substantially higher and more immediate risk of initiating KRT. The inclusion of such high-risk individuals is known to contribute to spectrum bias, potentially inflating performance metrics such as the AuROC. By including an analysis restricted to patients in CKD stages 3 and 4, we aimed to provide a more clinically meaningful assessment of the equation's performance in earlier and intermediate phases of disease progression. In this group, the formula maintained good predictive capacity, supporting its potential use in risk stratification, particularly relevant for guiding follow-up and timely referral for advanced care planning. Beyond spectrum bias, stage 5 patients may also differ systematically from earlier-stage patients in comorbidity burden, in the proportion already under structured pre-dialysis care, and in the timing of baseline creatinine relative to an evolving acute-on-chronic decline; these factors are partly addressed by restricting the analysis to stages 3–4 but remain a residual limitation.

In patients with DKD, the KFRE exhibited slightly higher discrimination compared with non-diabetic patients. This ability may be attributable to the higher prevalence of albuminuria in diabetic populations, a key predictor incorporated in the KFRE. Albuminuria reflects ongoing glomerular injury and is strongly associated with rapid CKD progression, thereby strengthening the predictive signal within the equation.[8,20] Discrimination was consistent regardless of how the diabetic subgroup was defined: using a broader definition based on the presence of diabetes irrespective of coded etiology (48.6% of the cohort), discrimination remained high (AuROC 0.90–0.92), reassuring against potential misclassification introduced by etiology coding.

Also, among patients with HF, the KFRE maintained high discrimination, although discrimination was lower in the 2-year prediction window. This observation is clinically coherent. In HF, the decision to initiate dialysis is often influenced not only by eGFR decline but by volume management needs and HF–related symptoms. Nevertheless, discrimination remained high in this subgroup, suggesting that the KFRE remains useful in the context of complex cardiorenal interactions.

Stratifying by ejection-fraction phenotype, discrimination was numerically lower in HFrEF than HFpEF, particularly at 2 years, although the small number of HFrEF patients

with documented ejection fraction limits the precision of this finding. Additionally, fluctuations in serum creatinine related to hemodynamic status, decongestion, and initiation of guideline-directed medical therapy (renin-angiotensin-aldosterone system inhibitors, SGLT2 inhibitors) may not reflect true nephron loss in HF patients and could confound KFRE performance in this subgroup.

Because standard survival analyses treat death as a censoring event, they may overestimate the risk of KRT in populations with substantial competing mortality, such as ours (19.0% mortality). We therefore repeated the analysis using a competing-risk framework: the overestimation from the naive approach was modest in our cohort, and the KFRE remained an independent predictor of KRT after accounting for death as a competing risk, while also being independently associated with mortality itself, indicating that death is a correlated competing risk in this population.

While discrimination (AuROC) was good, calibration analysis revealed that the KFRE overestimated risk in the highest-risk decile, consistent with overestimation previously reported in some European cohorts.[11] This suggests that, while the KFRE can adequately rank patients by relative risk, absolute risk estimates in the highest-risk stratum should be interpreted with some caution.

Patients who initiated KRT within 2 years were, paradoxically, younger and less likely to have dyslipidemia or atrial fibrillation than those who did not. Plausible explanations include preferential selection of younger, fitter patients for dialysis initiation while older or more comorbid patients die before reaching the KRT threshold (consistent with our competing-risk findings above); "reverse epidemiology" phenomena described in advanced CKD, whereby traditional cardiovascular risk factors are paradoxically associated with better short-term outcomes; and confounding by indication, whereby more comorbid patients are preferentially managed conservatively. These hypotheses warrant further investigation.

eGFR in this study was calculated using the 2009 CKD-EPI equation, consistent with the equation used in the original KFRE derivation and with the study's recruitment period (2012–2019). The 2021 CKD-EPI revision, which removed the race coefficient, may yield modestly different eGFR values. In our opinion, recalibration of the KFRE using the 2021 equation should be considered in future Portuguese validation studies.

These findings support the clinical use of KFRE for risk stratification in Portuguese CKD practice. Its consistent discrimination across major subgroups suggests that the KFRE may support timely nephrology referral, as well as early planning of KRT, including timely vascular access planning, preparation for dialysis modalities, and structured pre-dialysis education.[21,26–29] By moving beyond eGFR-only criteria, the KFRE helps avoid unnecessary referrals in elderly or frail patients with low progression risk, while enabling earlier intervention in high-risk individuals, thereby reinforcing adequate resource utilization. It also enhances patient counselling by providing clear, individualized estimates of kidney failure risk.

The strengths of this study include its large sample size, real-world clinical setting, and the comprehensive evaluation of KFRE performance across subgroups particularly relevant to CKD progression, including a formal competing-risk analysis. Limitations include its retrospective, single-centre design, which may limit generalisability given potential differences in referral patterns across the country; reliance on clinical coding and physician judgement (rather than systematic biopsy or echocardiographic criteria) for the classification of DKD and HF, respectively. Ejection fraction was documented in only 68% of HF patients; the absence of a biopsy-confirmed versus clinically-diagnosed DKD breakdown; missing data for some variables; and the lack of systematic coding for SGLT2 inhibitor use, which was not in routine use during most of the recruitment period.

CONCLUSION

The KFRE demonstrated good discrimination in predicting kidney failure risk in a large Portuguese CKD cohort, and discrimination remained high across key clinical subgroups. The slightly higher discrimination observed in diabetic kidney disease likely reflects the elevated albuminuria burden, while the preserved discrimination in heart-failure patients supports the utility of KFRE even when dialysis initiation is driven by volume and symptom-based considerations. These findings support the integration of KFRE into nephrology practice to guide referral, vascular access planning and pre-dialysis education, consistent with evidence from prior international studies[15,27,29] and latest guidelines.[21,30]

Acknowledgements

The authors would like to thank all colleagues from the Nephrology Department of Hospital Beatriz Ângelo for their support in data collection.

Awards and Previous Presentations

The results obtained have been presented at the Portuguese Nephrology Congress in Madeira, Portugal (Encontro Renal).

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship.
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).
Provenance and Peer Review: Not commissioned; externally peer-reviewed.

Contributorship Statement

ARA: Conceptualization. Methodology. Formal analysis: Investigation; Writing- Original Draft.
MSF: Conceptualization, Methodology. Formal analysis; Investigation.
BD: Methodology: Data collection; Formal analysis.
AF: Methodology: Data collection; Formal analysis.
SS: Conceptualization, Methodology, Investigation.
EA: Supervision; Writing- Reviewing and Editing.
LPF: Conceptualization; Methodology: Data collection; Investigation.
MR: Conceptualization, Methodology, Formal analysis: Investigation; Writing- Review & Editing.
All authors contributed to this work, approved the final version of the manuscript for publication, and agree to be accountable for all aspects of the work, ensuring the accuracy and integrity of the data presented.

REFERENCES

1. Ruiz-Ortega M, Rayego-Mateos S, Lamas S, Ortiz A, Rodrigues-Diez RR. Targeting the progression of chronic kidney disease. Nat Rev Nephrol. 2020;16:269–88. doi:10.1038/s41581-019-0248-y
2. Santos-Araújo C, Mendonça L, Carvalho DS, Bernardo F, Pardal M, Couceiro J, et al. Twenty years of real-world data to estimate chronic kidney disease prevalence and staging in an unselected population. Clin Kidney J. 2023;16:111–24. doi:10.1093/ckj/sfac206
3. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl. 2022;12:7-11. doi: 10.1016/j.kisu.2021.11.003.
4. Tangri N, Stevens LA, Griffith J, Tighiouart H, Djurdjev O, Naimark D, et al. A Predictive Model for Progression of Chronic Kidney Disease to Kidney Failure. JAMA. 2011;305:1553–9. doi:10.1001/jama.2011.451
5. Kwek JL, Pang HQJ, Li H, Lim WWL, Choo JCJ, Choong HL, et al. Validation of the kidney failure risk equation in predicting the risk of progression to kidney failure in a multi-ethnic Singapore chronic kidney disease cohort. Singapore Med J. 2022;63:313–8. doi:10.11622/smedj.2020170 (doi:10.11622/smedj.2020170)
6. Bravo-Zúñiga J, Chávez-Gómez R, Soto-Becerra P. Multicentre external validation of the prognostic model kidney failure risk equation in patients with CKD stages 3 and 4 in Peru: a retrospective cohort study. BMJ Open. 2024;14. 2024;14:e076217. doi:10.1136/bmjopen-2023-076217
7. Naranjo FS, Sang Y, Ballew SH, Stempniewicz N, Dunning SC, Levey AS, et al. Estimating Kidney Failure Risk Using Electronic Medical Records. Kidney360. 2021;2:415–24. doi:10.34067/KID.0005592020
8. Ramspek CL, Evans M, Wanner C, Drechsler C, Chesnaye NC, Szymczak M, et al. Kidney Failure Prediction Models: A Comprehensive External Validation Study in Patients with Advanced CKD. J Am Soc Nephrol. 2021;32:1174–86. doi:10.1681/ASN.2020071077
9. Tangri N, Grams ME, Levey AS, Coresh J, Appel LJ, Astor BC, et al. Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure. JAMA. 2016;315:164–74. doi:10.1001/jama.2015.18202
10. Major RW, Shepherd D, Medcalf JF, Xu G, Gray LJ, Brunskill NJ. The kidney failure risk equation for prediction of end stage renal disease in UK primary care: An external validation and clinical impact projection cohort study. PLoS Med. 2019;16:e1002955. doi:10.1371/journal.pmed.1002955
11. Escamilla-Cabrera B, Montomoli M, Kislikova M, de la Espada V, Olarte-García A, García-Prieto AM, et al. Validación multicéntrica de la fórmula Kidney Failure Risk Equation (KFRE) en pacientes españoles con enfermedad renal crónica avanzada. Nefrología. 2025;45:388–96. doi:10.1016/j.nefro.2025.02.004
12. Lennartz CS, Pickering JW, Seiler-Mußler S, Bauer L, Untersteller K, Emrich IE, et al. External Validation of the Kidney Failure Risk Equation and Re-Calibration with Addition of Ultrasound Parameters. Clin J Am Soc Nephrol. 2016;11:609-15. doi: 10.2215/CJN.08110715.
13. Irish GL, Cuthbertson L, Kitsos A, Saunder T, Clayton PA, Jose MD. The kidney failure risk equation predicts kidney failure: Validation in an Australian cohort. Nephrology. 2023;28:328–35. doi:10.1111/nep.14160
14. Wang Y, Nguyen FN, Allen JC, Lew JQL, Tan NC, Jafar TH. Validation of the kidney failure risk equation for end-stage kidney disease in Southeast Asia. BMC Nephrol. 2019;20:451. doi:10.1186/s12882-019-1643-0
15. Maher F, Teece L, Major RW, Bradbury N, Medcalf JF, Brunskill NJ, et al. Using the kidney failure risk equation to predict end-stage kidney disease in CKD patients of South Asian ethnicity: an external validation study. Diagn Progn Res. 2023;7:22. doi:10.1186/s41512-023-00157-x
16. Whitlock RH, Chartier M, Komenda P, Hingwala J, Rigatto C, Walld R, et al. Validation of the kidney failure risk equation in Manitoba. Can J Kidney Health Dis. 2017;4:2054358117705372. doi:10.1177/2054358117705372
17. Sullivan MK, Jani BD, Rutherford E, Welsh P, McConnachie A, Major RW, et al. Potential impact of NICE guidelines on referrals from primary care to nephrology: A primary care

database and prospective research study. Br J Gen Pract. 2023;73:E141–7. doi:10.3399/BJGP.2022.0145
18. da Silva BM, Charreu J, Duarte I, Outerelo C, Gameiro J. Validation of the kidney failure risk equation in a Portuguese cohort. Nefrología. 2023;43:467–73. doi:10.1016/j.nefroe.2022.03.007
19. Rozi NR, Selvaraj CS, Tan JK, Lim ZF, Nordin NW, Mazhar NH, et al. Kidney failure risk equation (KFRE), A risk-based triage for nephrology referrals: A mixed-methods study at pre-implementation phase among healthcare providers. Prim Care Diabetes. 2025;19:636–45. doi:10.1016/j.pcd.2025.08.001
20. Goubar A, Mangelis A, Thomas S, Fountoulakis N, Collins J, Ayis S, et al. Investigation of end-stage kidney disease risk prediction in an ethnically diverse cohort of people with type 2 diabetes: use of kidney failure risk equation. BMJ Open Diabetes Res Care. 2024;12:e004282. doi:10.1136/bmjdrc-2024-004282
21. Stevens PE, Ahmed SB, Carrero JJ, Foster B, Francis A, Hall RK, et al. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024;105:S117–314. doi:10.1016/j.kint.2023.10.018
22. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604-12. doi:10.7326/0003-4819-150-9-200905050-00006. Erratum in: Ann Intern Med. 2011;155:408.
23. Thanabalasingam SJ, Iliescu EA, Norman PA, Day AG, Akbari A, Hundemer GL, et al. Independent External Validation and Comparison of Death and Kidney Replacement Therapy Prediction Models in Advanced CKD. Kidney Med. 2022;4:100440. doi:10.1016/j.xkme.2022.100440
24. Walker H, Khan S, Padmanabhan S, Pell JP, Lewsey J, Mackay D, et al. Analysis of the kidney failure risk equation implementation in routine clinical practice and health inequalities in chronic kidney disease care: a retrospective cohort study. BMC Nephrol. 2025;26:113. doi:10.1186/s12882-025-04043-0
25. Ingwiller M, Keller N, Krummel T, Prinz E, Steinmetz L, Hannedouche T, et al. Enhancing vascular access planning in CKD: validating the 40% KFRE threshold for predicting ESKD in a French retrospective cohort study. Clin Kidney J. 2024;17:sfae220. doi:10.1093/ckj/sfae220
26. O'Hare AM, Bertenthal D, Walter LC, Garg AX, Covinsky K, Kaufman JS, et al. When to refer patients with chronic kidney disease for vascular access surgery: Should age be a consideration? Kidney Int. 2007;71:555–61. doi:10.1038/sj.ki.5002078
27. da Silva BM, Gameiro J. Generalize the use of the kidney failure risk equation (KFRE) for better vascular access planning. Clin Kidney J. 2024;17:sfae060. doi: 10.1093/ckj/sfae060.
28. Hahn Lundström U, Ramspek CL, Dekker FW, van Diepen M, Carrero JJ, Hedin U, et al. Clinical impact of the Kidney Failure Risk Equation for vascular access planning. Nephrol Dial Transplant. 2024;39:2079-87. doi: 10.1093/ndt/gfae064.
29. Lo R, Narasaki Y, Lei S, Rhee CM. Management of traditional risk factors for the development and progression of chronic kidney disease. Clin Kidney J. 2023;16:1737-50. doi: 10.1093/ckj/sfad101.
30. National Institute for Health and Care Excellence (NICE). Chronic kidney disease: assessment and management (NICE guideline NG203) [accessed Jan 2026] Available at: https://www.nice.org.uk/guidance/ng203

SUPPLEMENTARY MATERIAL

Table S1. Patient flow and reasons for exclusion

Category	N	% of excluded (N=1264)
CKD stage 1–2 (outside eligibility criteria)	780	61.7%
CKD stage 3–5, missing baseline urine ACR (KFRE-required variable)	205	16.2%
CKD stage 3–5, insufficient follow-up for the progression analysis	279	22.1%
Total excluded	1264	100%

Table S2. Competing-risk analysis: naive versus true cumulative incidence of KRT

Horizon	Naive (1–KM) %	True CIF (competing risk) %
2-year	4.84	4.77
5-year	8.65	8.39

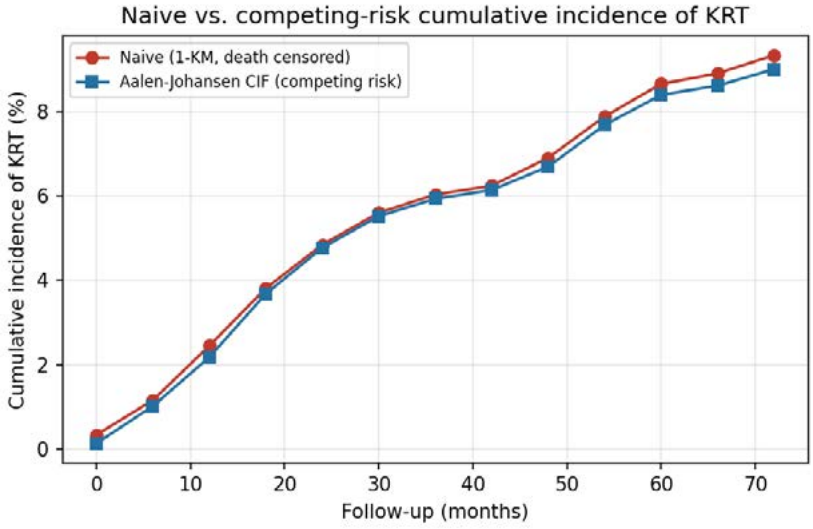


Figure S1. Naive versus competing-risk cumulative incidence of kidney replacement therapy (KRT)

Table S3. Cause-specific Cox models for KRT and death

Outcome	Predictor	N events	HR (95% CI)	*p*
KRT (death censored)	2-year KFRE risk	178	1.056 (1.050–1.061)	<0.001
KRT (death censored)	5-year KFRE risk	178	1.044 (1.040–1.048)	<0.001
Death (KRT censored)	2-year KFRE risk	279	1.016 (1.006–1.026)	0.001
Death (KRT censored)	5-year KFRE risk	279	1.009 (1.004–1.015)	<0.001

N=1469 unique patients with complete follow-up data. Proportional-hazards assumption satisfied for both cause-specific models (Schoenfeld residuals, p>0.05).

Table S4. Calibration: predicted versus observed risk by decile

Decile	N	2-yr predicted (%)	2-yr observed CIF (%)	5-yr predicted (%)	5-yr observed CIF (%)
1	147	0.1	0.7	0.3	0.7
2	147	0.2	0.7	0.7	0.7
3	147	0.4	0.0	1.4	0.0
4	147	0.6	0.7	2.3	0.7
5	147	1.1	1.4	4.0	2.1
6	146	1.8	3.4	6.7	4.8
7	147	2.9	0.7	10.7	2.8
8	147	5.4	0.7	19.4	3.5
9	147	12.5	5.4	39.7	13.8
10	147	45.5	32.7	84.7	53.3

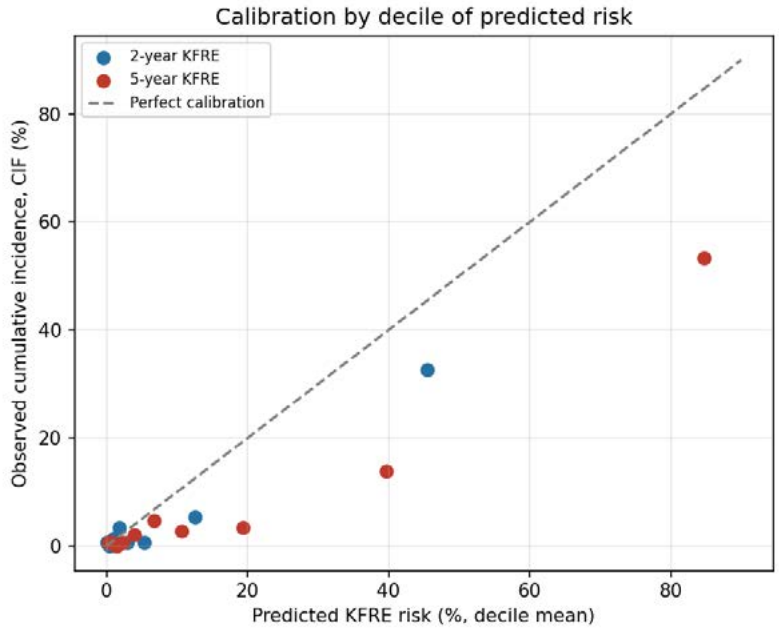


Figure S2. Calibration plot: predicted versus observed risk by decile, at 2 and 5 years

Table S5. KFRE discrimination by DKD definition (etiology-based vs broad diabetes-based)

Definition	N (2-yr)	AuROC 2-yr	N (5-yr)	AuROC 5-yr
DKD, etiology-based (N=550, 31.6%)	462	0.918	218	0.942
Diabetes, broad definition (N=846, 48.6%)	698	0.900	318	0.917

Table S6. KFRE discrimination by heart failure phenotype

HF phenotype	N (2-yr)	Events (2-yr)	AuROC 2-yr	N (5-yr)	Events (5-yr)	AuROC 5-yr
HF, overall	405	40	0.873	174	62	0.906
HFrEF (LVEF<40%)	45	7	0.767	20	10	0.870
HFpEF (LVEF≥50%)	179	18	0.872	75	31	0.938

Ejection fraction documented in 342/502 HF patients (68.1%): HFrEF 16.7%, HFmrEF 16.7%, HFpEF 66.7%. HFmrEF omitted from stratified AuROC owing to insufficient events.

Table S7. Overlap between DKD and heart failure (N=1741)

	HF absent	HF present	Total
DKD absent (etiology-based)	878	313	1191
DKD present (etiology-based)	361	189	550
Total	1239	502	1741

189 patients (10.9%) had both DKD and HF. Of the 313 HF patients without a DKD etiology code, 112 (35.8%) were nonetheless diabetic under the broad definition.

Table S8. Univariable screen for candidate multivariable covariates (2-year horizon)

Covariate	N	HR	*p*
Age	1609	0.964	<0.001
Weight (kg)	1538	0.984	0.007
Black race	1585	3.210	<0.001
Smoking	1322	1.830	0.005
BMI >25 kg/m²	1539	0.706	0.039
Hypertension	1609	0.774	0.276 (NS)
Dyslipidemia	1609	0.578	0.001
Atrial fibrillation	1609	0.419	0.011

Table S9. Exploratory multivariable Cox model for KRT initiation

Covariate	2-yr HR (95% CI)	2-yr *p*	5-yr HR (95% CI)	5-yr *p*
KFRE-predicted risk	1.058 (1.050–1.066)	<0.001	1.039 (1.034–1.044)	<0.001
Black race	1.734 (0.891–3.375)	0.105	1.428 (0.816–2.497)	0.212
Smoking	1.334 (0.805–2.210)	0.263	0.965 (0.649–1.435)	0.860
BMI >25 kg/m²	0.936 (0.602–1.455)	0.769	1.156 (0.806–1.659)	0.430
Dyslipidemia	0.857 (0.553–1.327)	0.489	0.745 (0.526–1.055)	0.097
Atrial fibrillation	0.530 (0.191–1.471)	0.223	0.799 (0.411–1.552)	0.507
Hypertension	1.815 (0.901–3.656)	0.095	1.297 (0.726–2.318)	0.379

N=1060 (2-year, 91 events); N=439 (5-year, 140 events); complete cases. Exploratory analysis, not part of the external validation of the KFRE. Age was excluded as a direct KFRE component; hypertension retained for clinical relevance despite univariable non-significance. Proportional-hazards assumption satisfied for both models.

Table S10. Baseline medication use

Medication	Full cohort (N=1741)	DKD subgroup (N=550)	HF subgroup (N=502)
Statin	31.4%	34.8%	37.2%
RAASi (ACEi/ARB)	61.7%	67.3%	63.7%
Loop diuretic	43.1%	54.5%	68.1%
Thiazide	18.4%	16.4%	12.7%
Potassium-sparing diuretic	2.2%	2.2%	4.4%

SGLT2 inhibitors were not in routine use during most of the recruitment period (2012–2019) and are not separately coded.

Table S11. Full breakdown of CKD etiologies (N=1741)

Etiology	N	%
Diabetes mellitus (DKD)	550	31.6%
Ischemic/hypertensive nephrosclerosis	531	30.5%
Other/unknown	225	12.9%
Chronic glomerulonephritis	140	8.0%
Uropathy	102	5.9%
No indication/unspecified	85	4.9%
Nephrolithiasis	69	4.0%
Polycystic kidney disease	34	2.0%
Other	5	0.3%