

ORIGINAL ARTICLE

Which equation and which biomarker should be used in the Kidney Failure Risk Equation? A comparative analysis in the CKD-REIN cohort

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ABSTRACT

Background. The Kidney Failure Risk Equation (KFRE) is a widely used tool to estimate the 2- and 5-year risk of progression to kidney failure in patients with chronic kidney disease (CKD). The choice of estimated glomerular filtration rate (eGFR) equation and biomarker may influence its prognostic performance. We aimed at comparing the predictive performance of the KFRE when used with different eGFR equations [CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) vs. EKFC (European Kidney Function Consortium)] and biomarkers (creatinine, cystatin C, or both) in a large French CKD cohort.

Methods. We analyzed 2168 patients with CKD stages G3–G5 from the prospective Chronic Kidney Disease Renal Epidemiology and Information Network cohort. Eight eGFR equations were evaluated in combination with both the four- and eight-variable KFRE models. Prognostic performance was assessed at 2 and 5 years using the time-dependent area under the receiver operating characteristic curve (AUROC), Brier scores, calibration plots, and decision curve analysis. Subgroup analyses were performed by age and sex.

Results. Discrimination was uniformly high (AUROC > 0.89), but calibration patterns and decision curve analyses differed between equations. The creatinine-based CKD-EPI 2009 equation demonstrated robust and consistent performance across models and time horizons. EKFC equations—especially when using creatinine alone—showed

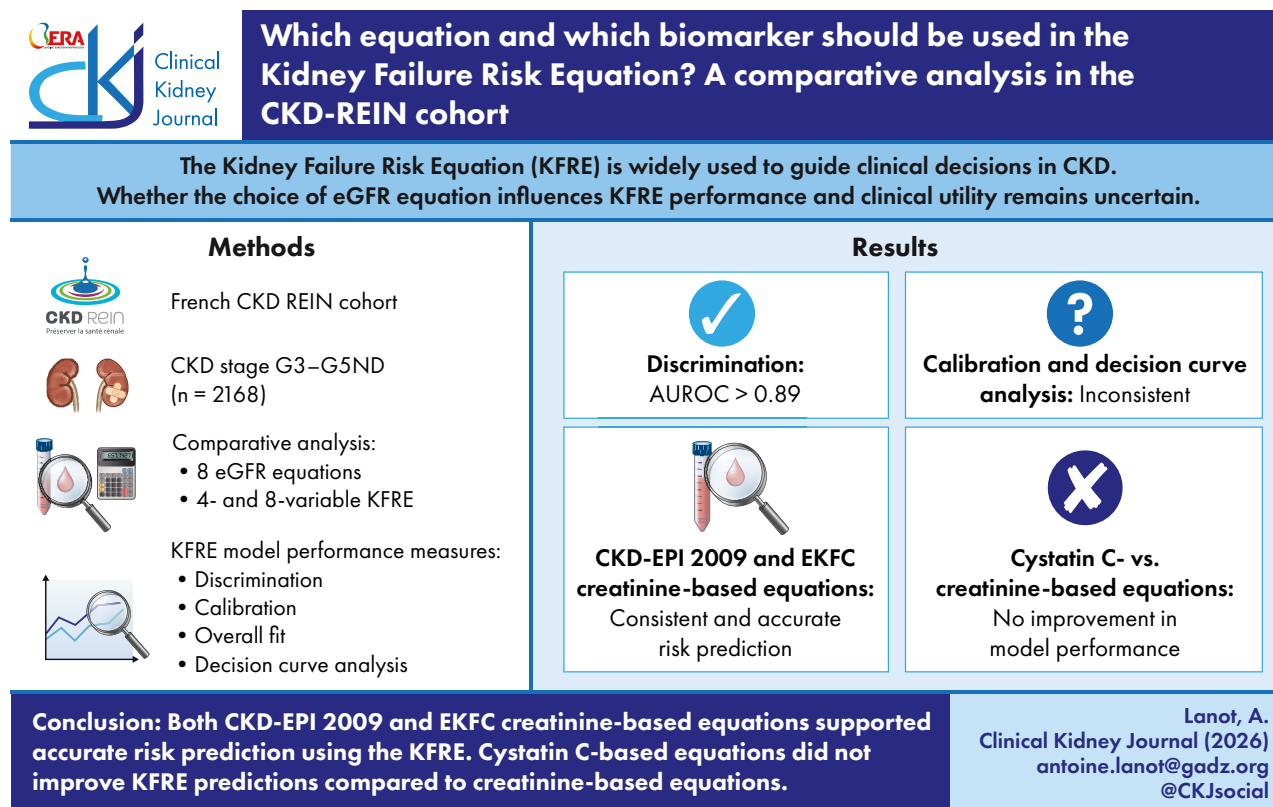
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slightly improved clinical utility at the 40% decision threshold. Cystatin C-based equations did not improve KFRE predictions compared to creatinine-based ones.

Conclusions. In this French CKD cohort, both CKD-EPI 2009 and EKFC creatinine-based equations supported accurate risk prediction using the KFRE. These findings support the use of EKFC in European clinical practice and reinforce the importance of aligning eGFR equations with the population context when applying prognostic models.

GRAPHICAL ABSTRACT



Keywords: chronic kidney disease, eGFR, EKFC, KFRE, kidney failure

KEY LEARNING POINTS

What was known:

- The Kidney Failure Risk Equation (KFRE) is widely used to estimate risk of kidney failure. It was originally developed using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 equation, but the impact of using newer estimated glomerular filtration rate (eGFR) equations, particularly European Kidney Function Consortium (EKFC), on KFRE performance in European populations remains unclear.

This study adds:

- In a large French CKD cohort, the creatinine-based EKFC equation performed as well as CKD-EPI 2009 within the KFRE framework, including in clinical decision-making thresholds. The use of cystatin C, alone or combined, did not improve prediction of kidney failure at 2 or 5 years.

Potential impact:

- These findings support the use of creatinine-based EKFC for both GFR estimation and risk prediction in European practice. Aligning KFRE with EKFC may facilitate unified, race-free clinical tools while maintaining prognostic accuracy in risk-based decision-making for CKD progression.

INTRODUCTION

The Kidney Failure Risk Equation (KFRE) is a widely used prognostic tool designed to estimate the 2- or 5-year risk of progression to kidney failure, based on either four or eight variables [1, 2]. Among these variables, the estimated glomerular filtration rate (eGFR) plays a central role [3]. The original KFRE was developed using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 equation to estimate eGFR [4]. However, several new eGFR equations have emerged since, and the optimal formula to use in clinical practice remains debated [5]. Beyond discrimination, calibration and clinical utility at fixed decision thresholds may be critical when KFRE is used to guide clinical care.

In 2012, new CKD-EPI equations were implemented using cystatin C and the combination of creatinine and cystatin C [6]. CKD-EPI 2021 equations, introduced as race-free alternatives, perform less well than CKD-EPI 2009/2012 in European populations [7]. The European Kidney Function Consortium (EKFC) equations provide a race-free approach to GFR estimation using population-specific normalization factors and are now recommended for use in white European populations [5, 8–10].

Creatinine is widely available but affected by non-GFR determinants, whereas cystatin C offers an alternative biomarker and has been associated with overall and cardiovascular mortality [5, 9, 11, 12].

Whether substituting EKFC for CKD-EPI within the KFRE framework maintains or compromises prognostic performance remains an open question. In this context, our aim was to compare the prognostic performance of KFRE when using different combinations of eGFR equations (CKD-EPI vs. EKFC) and biomarkers (creatinine, cystatin C, or both) in a large, contemporary French CKD cohort.

MATERIALS AND METHODS

Study population

We used data from the Chronic Kidney Disease Renal Epidemiology and Information Network (CKD-REIN) cohort study (ClinicalTrials.gov Identifier, NCT03381950). CKD-REIN is a prospective cohort conducted in 40 nationally representative nephrology outpatient clinics in France, in which patients aged 18 years old or more, with CKD stages G3 to G5ND (eGFR < 60 ml/min/1.73 m², not previously treated with maintenance dialysis or kidney transplantation) were included. From July 2013 to March 2016, 3033 patients were included during a routine nephrology visit. The French National Institute of Health and Medical Research institutional review board (IRB00003888) and ethics committee (CCTIRS12.360/PPP) approved the CKD-REIN study. Details about the study protocol were published previously [13].

Demographic, clinical, and laboratory data

Demographic, clinical, and laboratory data were collected at baseline and then annually for 5 years through patient interviews and review of medical records. Baseline data included sociodemographic and comorbidities such as hypertension, diabetes, and cardiovascular disease. Fasting blood samples were processed and stored centrally according to standardized procedure. Serum cystatin C level was determined with centralized immune-turbidimetry method. Urinary albumin-to-creatinine ratio (ACR) were measured or estimated from protein-to-creatinine ratio [14].

Estimated GFR equations

Estimated GFR was calculated using multiple equations: creatinine-based EKFC, cystatin C-based EKFC, the mean of both EKFC estimates, creatinine-based CKD-EPI 2009, cystatin C-based CKD-EPI 2012, creatinine and cystatin C CKD-EPI 2012, creatinine-based CKD-EPI 2021, and creatinine and cystatin C CKD-EPI 2021. In a complementary analysis, cystatin C-based EKFC was also computed using sex-specific Q-values [4, 8, 9, 12]. The race coefficient included in the CKD-EPI 2009 and 2012 versions was not used since it was shown from European data that this US racial coefficient tended to heavily overestimate the eGFR in African and Black European subjects [5, 15–18]. The eGFR equations used are provided in Supplementary Materials (Supplementary Table S1).

Kidney Failure Risk Equation

The KFREs were calculated at 2- and 5-year horizon, using both the four- and eight-variable models in their regional calibrated non-North America version, as described by Tangri et al. [2] and reported in Supplementary Materials (Supplementary Table S2).

Kidney failure data

Kidney failure and deaths were identified from records and confirmed via linkage to national registries. Patients were censored at the date of death, completion of the 5-year follow-up by clinical research associates, administrative censoring date on December 2020, or study withdrawal.

Statistical analyses

Continuous variables were described as median and interquartile ranges (IQR), and categorical variables as counts and percentages. Restricted mean survival time (RMST) at 2 and 5 years was estimated using Kaplan–Meier methods [19].

We modeled median eGFR values as a function of patient age using quantile regression with restricted cubic splines to visualize systematic differences between the different equations.

We assessed the prognostic performance of the KFRE for 2- and 5-year kidney failure onset using the aforementioned combinations of eGFR equations and biomarkers.

Discrimination was evaluated using time-dependent area under the receiver operating characteristic curve (AUROC) with inverse probability of censoring weighting (IPCW)-derived confidence intervals [20].

Calibration was assessed by plotting observed versus predicted risks by deciles of KFRE-predicted probabilities [21].

Overall predictive performance was evaluated using time-dependent Brier scores with IPCW, with model comparisons based on paired bootstrap resampling. Lower Brier score indicates better predictive accuracy [22, 23].

Decision curve analysis (DCA) was performed to assess clinical utility across risk thresholds without formal statistical testing. The net benefit combines the proportion of true positives and false positives, weighted by the threshold probability, which reflects the harm of unnecessary treatment versus missed events. Higher net benefit indicates better clinical utility [24].

Subgroup analyses were conducted in groups of patients aged ≥65 and <65 years, and according to sex. A complementary analysis was performed including sex-specific Q-value for cystatin C-based EKFC.

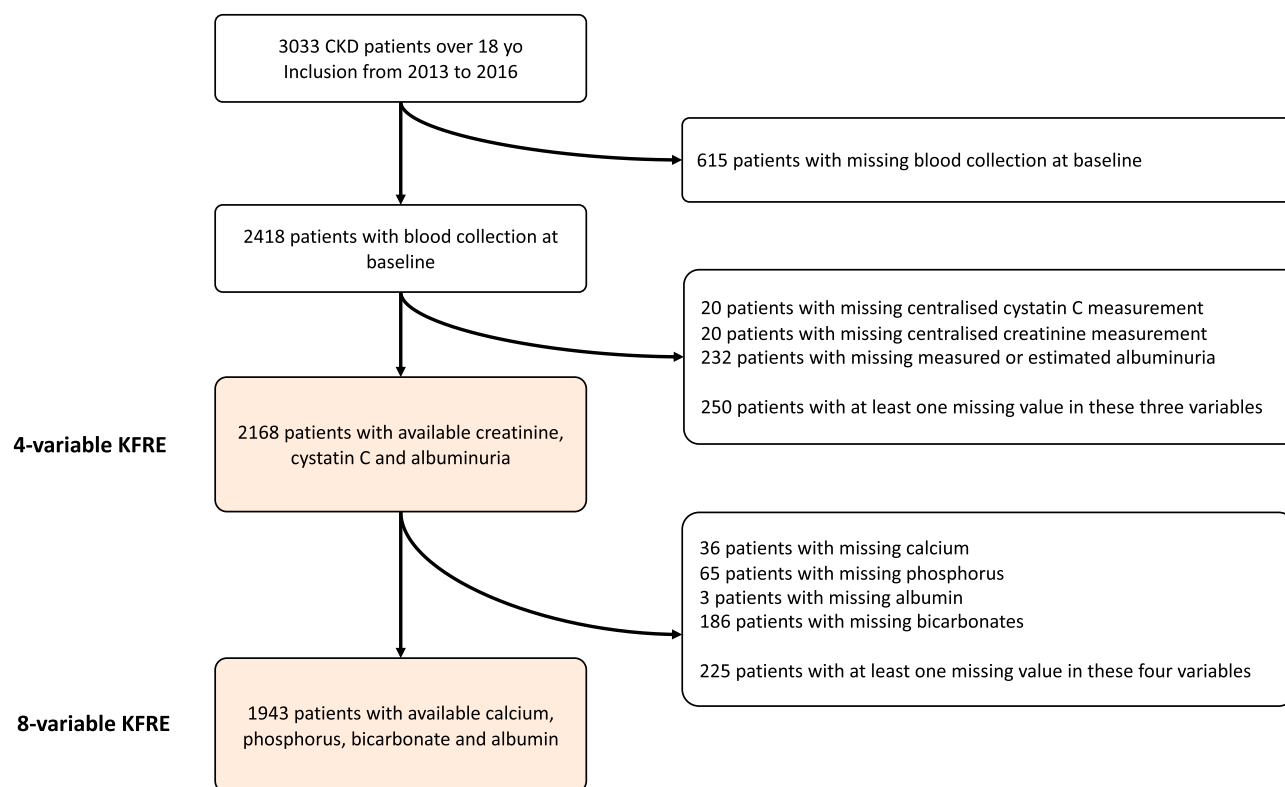


Figure 1: Flowchart.

Missing data were supposed to be missing completely at random, and analyses were restricted to complete cases, with exclusion of individuals with missing data. Statistical analyses were performed using R software version 3.6.1 (R foundation for Statistical Computing, Vienna, Austria).

This study was reported in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis statement [25] (Supplementary Table S3).

RESULTS

The study size was determined by the number of eligible patients available in the CKD-REIN cohort with complete baseline data required for KFRE computation. From the 3033 patients included in the CKD-REIN cohort, 615 did not undergo blood collection at baseline, and 250 had missing baseline information on either serum creatinine, serum cystatin C, or ACR, leaving 2168 patients for the four-variable KFRE score analysis. Two hundred and twenty-five patients had at least one missing data across serum calcium, phosphorus, albumin, or bicarbonates, and were therefore excluded for the analyses of the eight-variable KFRE, with 1943 remaining patients (Fig. 1).

The median age was 68 years (IQR: 60–76) and 1453 (67%) patients were male. The prevalence of diabetes mellitus and hypertension was 41.7% and 90.6%, respectively. Patients had a history of cardiovascular event in 1127 (52%) cases. Regarding albuminuria, 816 (37.6%) patients were classified A3 stage with an ACR >300 mg/g, while 754 (34.8%) were in stage A2 (ACR between 30 and 300 mg/g), and 598 (27.6%) were in stage A1, with an ACR <30 mg/g. Characteristics of the population are shown in Table 1. The characteristics of non-included patients were comparable to those of included ones (Supplementary Table S4).

Table 1: Characteristics of the population.

	Overall (N = 2168)
Female sex, n (%)	715 (33)
Age, median (IQR)	68.0 (60.0–76.0)
BMI, median (IQR)	28.0 (24.8–31.9)
Missing, n (%)	35 (1.6)
Hypertension, n (%)	1965 (90.6)
Missing, n (%)	5 (0.2)
Diabetes mellitus	903 (41.7)
Missing, n (%)	5 (0.2)
Cardiovascular history, n (%)	1127 (52.0)
Missing, n (%)	11 (0.5)
Creatinine (μmol/l), median (IQR)	170.9 (138.0–223.0)
Cystatin C (mg/l), median (IQR)	2.3 (1.8–2.9)
ACR (mg/mmol), median (IQR)	129.8 (24.8–658.0)
ACR stage	
A1, n (%)	598 (27.6%)
A2, n (%)	754 (34.8%)
A3, n (%)	816 (37.6%)
Albuminemia (g/l), median (IQR)	40.8 (38.3–43.1)
Missing, n (%)	3 (0.1%)
Phosphatemia (mmol/l), median (IQR)	1.0 (1.1–1.3)
Missing, n (%)	65 (3.0%)
Serum bicarbonates (mmol/l), median (IQR)	25.0 (23.0–27.0)
Missing, n (%)	186 (8.6%)
Calcemia (mmol/l), median (IQR)	2.4 (2.3–2.4)
Missing, n (%)	36 (1.7%)

IQR: interquartile range; BMI: body mass index; ACR: albumin-to-creatinine ratio.

Table 2: Distribution of the eGFR according to the different equations used.

Equation	Biomarker	Min	Q1	Median	Mean	Q3	Max
EKFC	Creatinine	8.69	23.21	31.39	32.40	40.2	76.24
	Cystatin C	10.01	22.52	29.11	30.74	37.57	88.39
	Creatinine and cystatin C	9.46	23.16	30.23	31.57	38.72	73.50
CKD-EPI 2009/2012	Creatinine	8.27	23.00	31.73	32.74	40.85	79.27
	Cystatin C	6.83	18.55	25.00	26.96	33.34	87.58
	Creatinine and cystatin C	7.08	20.47	27.95	29.68	37.37	79.35
CKD-EPI 2021	Creatinine	8.95	24.84	34.04	35.14	43.82	84.52
	Creatinine and cystatin C	7.35	21.31	29.02	30.84	38.93	84.26

Min: minimum; Q1: first quartile; Q3: third quartile; Max: maximum; EKFC: European kidney function consortium; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.

The median eGFR varied depending on the equation and biomarker used (Table 2). Across the whole spectrum of age, median eGFR was higher considering creatinine-based CKD-EPI 2021 (Supplementary Fig. S1).

Kidney failure occurred in 210 patients at 2 years and in 501 patients at 5 years from the study inclusion. RMST without kidney failure or death was 1.85 years (95% CI: 1.83, 1.87) at 2 years and 4.02 years (95% CI: 3.95, 4.08) at 5 years. The distribution of the KFRE scores showed a constant pattern with high density of values concentrated in the lower probability range (Supplementary Fig. S2).

Despite uniformly high AUROC values, subsequent analyses showed equation-specific differences in calibration and clinical utility, indicating that high discrimination does not imply full interchangeability.

Five-year risk of kidney failure with four-variable KFRE

The discriminative power for the risk of kidney failure at 5 years was high, with time-dependent AUROCs ranging from 0.890 (95% CI: 0.873–0.905) with use of cystatin C-based EKFC to 0.900 (95% CI: 0.886–0.915) with combined creatinine and cystatin C-based CKD-EPI 2021 (Table 3). Pairwise comparisons of the AUROC for the four-variable KFRE models at 5 years revealed no statistically significant difference, with almost overlapping ROC curves (Fig. 2a).

Visually, the calibration curves were best fitted for creatinine-based CKD-EPI 2009 and EKFC's equations, while combined-based CKD-EPI and cystatin C-based CKD-EPI 2012 equations tended to overestimate the kidney failure risk at 5 years (Fig. 2b).

There was no significant difference in the Brier scores obtained with creatinine-based EKFC and CKD-EPI 2009 equations, and both outperformed creatinine-based CKD-EPI 2021. Considering cystatin C, no difference in Brier scores emerged when EKFC was compared to CKD-EPI 2012. The combined CKD-EPI equations outperformed combined EKFC equations.

EKFC equations based on cystatin C alone or in combination with creatinine showed similar performance compared to the creatinine-based EKFC. No significant difference in Brier scores was observed between the creatinine-based CKD-EPI 2009 and the cystatin C-based CKD-EPI 2012 equation whereas the performance was lower than combined CKD-EPI 2012 or combined 2021 equations (Fig. 2c).

Five-year risks of kidney failure with eight-variable KFRE

Discrimination of the eight-variable KFRE at 5 years was high across all equations, with time-dependent AUROC ranging from 0.895 (95% CI: 0.878; 0.912) when using creatinine-based EKFC

and creatinine-based CKD-EPI 2009, to 0.903 (95% CI: 0.886; 0.919) when using creatinine and cystatin C-based CKD-EPI 2021 (Table 3).

ROC curves were similar, with no significant differences between eight-variable KFRE models at 5 years when compared pairwise (Fig. 3a).

Calibration curves showed that the curves globally followed the diagonal, indicating satisfactory calibration, with slight visible deviations such as overestimation at higher risk levels for all models but cystatin C-based CKD-EPI 2012, which showed a tendency for underestimation of the risk (Fig. 3b).

Brier scores were consistently low across models, ranging from 0.118 (95% CI: 0.107; 0.129) for creatinine-based CKD-EPI 2021 to 0.107 (95% CI: 0.098; 0.117) for creatinine and cystatin C-based CKD-EPI 2012 (Table 3). When creatinine was used as a biomarker, the CKD-EPI 2009 equation significantly outperformed EKFC, which was superior to CKD-EPI 2021. Cystatin C-based CKD-EPI 2012 was more accurate than cystatin C-based EKFC. The combined CKD-EPI equations outperformed combined EKFC equations. EKFC equations based on cystatin C alone or in combination with creatinine showed significantly lower performance compared to the creatinine-based EKFC. No significant difference in Brier scores was observed between the creatinine-based CKD-EPI 2009 and the cystatin C-based or combined CKD-EPI 2012 or CKD-EPI 2021 equations (Fig. 3c).

Two-year risk of kidney failure with four- and eight-variable KFRE

The time-dependent AUROCs for both the four- and eight-variable KFRE models at 2 years were good to excellent (Table 3). All models showed similar discriminative performance, with no significant pairwise differences in AUROC at either time point (Supplementary Figs S3A and S4A). Calibration was globally poorer with the eight-variable models compared to their four-variable counterparts (Supplementary Figs S3B and S4B and Table 3).

The pattern of differences between the eight-variable models largely mirrored those observed with the four-variable versions. Among creatinine-based equations, CKD-EPI 2009 outperformed EKFC, and both performed better than CKD-EPI 2021.

The cystatin C-based CKD-EPI 2012 equation was associated with significantly higher Brier scores compared to the creatinine-based EKFC in the eight-variable KFRE setting, while no such difference was observed in the four-variable models.

When using combined biomarkers, the CKD-EPI 2012 equation yielded better overall predictive accuracy than CKD-EPI 2021, as reflected by lower Brier scores (Supplementary Figs S3C and S4C).

Table 3: AUROC values and Brier scores.

Model	Equation		AUROC, [95% CI]	Brier score, [95% CI]
Four-variable KFRE 5-year risk	EKFC	Creatinine	0.893, [0.877–0.909]	0.111, [0.101–0.121]
		Cystatin C	0.890, [0.873–0.905]	0.113, [0.103–0.122]
		Creatinine and cystatin C	0.898, [0.884–0.914]	0.109, [0.100–0.119]
	CKD-EPI 2009/2012	Creatinine	0.892, [0.874–0.908]	0.111, [0.101–0.120]
		Cystatin C	0.891, [0.875–0.907]	0.111, [0.103–0.120]
		Creatinine and cystatin C	0.900, [0.884–0.915]	0.105, [0.096–0.114]
	CKD-EPI 2021	Creatinine	0.892, [0.875–0.908]	0.115, [0.105–0.125]
		Creatinine and cystatin C	0.900, [0.886–0.915]	0.106, [0.097–0.115]
Eight-variable KFRE 5-year risk	EKFC	Creatinine	0.895, [0.878–0.912]	0.114, [0.104–0.125]
		Cystatin C	0.897, [0.881–0.913]	0.115, [0.104–0.125]
		Creatinine and cystatin C	0.902, [0.886–0.918]	0.113, [0.103–0.123]
	CKD-EPI 2009/2012	Creatinine	0.895, [0.878–0.912]	0.113, [0.103–0.124]
		Cystatin C	0.897, [0.881–0.913]	0.110, [0.100–0.119]
		Creatinine and cystatin C	0.902, [0.887–0.918]	0.107, [0.098–0.117]
	CKD-EPI 2021	Creatinine	0.895, [0.879–0.911]	0.118, [0.107–0.129]
		Creatinine and cystatin C	0.903, [0.886–0.919]	0.109, [0.099–0.119]
Four-variable KFRE 2-year risk	EKFC	Creatinine	0.900, [0.879–0.920]	0.063, [0.055–0.070]
		Cystatin C	0.896, [0.876–0.915]	0.066, [0.058–0.074]
		Creatinine and cystatin C	0.904, [0.883–0.923]	0.064, [0.056–0.072]
	CKD-EPI 2009/2012	Creatinine	0.900, [0.878–0.919]	0.062, [0.054–0.069]
		Cystatin C	0.896, [0.876–0.916]	0.064, [0.057–0.071]
		Creatinine and cystatin C	0.906, [0.886–0.925]	0.061, [0.054–0.068]
	CKD-EPI 2021	Creatinine	0.901, [0.878–0.921]	0.063, [0.055–0.071]
		Creatinine and cystatin C	0.907, [0.887–0.925]	0.061, [0.054–0.069]
Eight-variable KFRE 2-year risk	EKFC	Creatinine	0.905, [0.882–0.925]	0.065, [0.057–0.074]
		Cystatin C	0.903, [0.881–0.922]	0.068, [0.059–0.077]
		Creatinine and cystatin C	0.908, [0.886–0.929]	0.067, [0.058–0.075]
	CKD-EPI 2009/2012	Creatinine	0.904, [0.880–0.924]	0.065, [0.056–0.073]
		Cystatin C	0.903, [0.880–0.923]	0.064, [0.056–0.072]
		Creatinine and cystatin C	0.910, [0.888–0.930]	0.063, [0.055–0.071]
	CKD-EPI 2021	Creatinine	0.905, [0.882–0.926]	0.066, [0.057–0.075]
		Creatinine and cystatin C	0.910, [0.889–0.929]	0.064, [0.056–0.072]

KFRE: Kidney Failure Risk Equation; EKFC: European Kidney Function Consortium; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; AUROC: area under the receiver operating curve.

Decision curve analysis

DCA should focus on prespecified thresholds of clinical relevance. In line with KDIGO 2024 recommendations, we examined two key thresholds for the 2-year risk of kidney failure: 10%, used to guide transitions from nephrology to interprofessional care, and 40%, which informs patient education, preparation for kidney replacement therapy, vascular access planning, or transplant referral. Between 10% and 15%, all models demonstrated grossly overlapping net benefit curves, with no clear superiority. However, from 40% to 60%, the EKFC creatinine-based model exhibited a slightly higher net benefit, whereas models using cystatin C—particularly EKFC and CKD-EPI 2021—showed consistently lower net benefit across a wide range of thresholds (20%–70%) (Fig. 4).

In the eight-variable KFRE versions, no substantial differences in net benefit were observed at these decision thresholds except lower net benefit for cystatin C-based EKFC and CKD-EPI 2021 models (Supplementary Fig. S5).

Subgroup analyses

Discrimination of the various KFRE versions was slightly higher in females than in males in sex-stratified analyses, although no significant differences in AUROCs were observed (Supplementary Table S5). Calibration curves did not appear to differ between males and females (Supplementary Fig. S6). Brier scores

were consistently lower in males than in females. The pattern of Brier score differences between KFRE models remained consistent with the overall population, but notably the cystatin C-based models for the 2-year risk performed worse in women than in men (Supplementary Fig. S7).

AUROCs values were marginally higher in patients over 65 years of age, but no statistically significant differences were found between models (Supplementary Table S6). Calibration curves distribution were similar across both age groups (Supplementary Fig. S8). The superior performance of the creatinine-based CKD-EPI 2009 equation compared to the EKFC was most pronounced in individuals over 65 years (Supplementary Fig. S9).

The AUROCs obtained using the cystatin C-based EKFC equation with sex-specific Q-value were similar to those obtained with the sex-independent version. However, analysis of Brier scores revealed two notable differences: in contrast to the main analysis, the sex-specific EKFC equation performed significantly worse than the cystatin C-based CKD-EPI 2012 equation when predicting 5-year risk with the four-variable KFRE and 2-year risk with the eight-variable KFRE, both in favor of CKD-EPI 2012 (Supplementary Tables S7 and S8).

DISCUSSION

Using a large representative French CKD cohort, we found that the performance of the KFRE score is sensitive to the choice

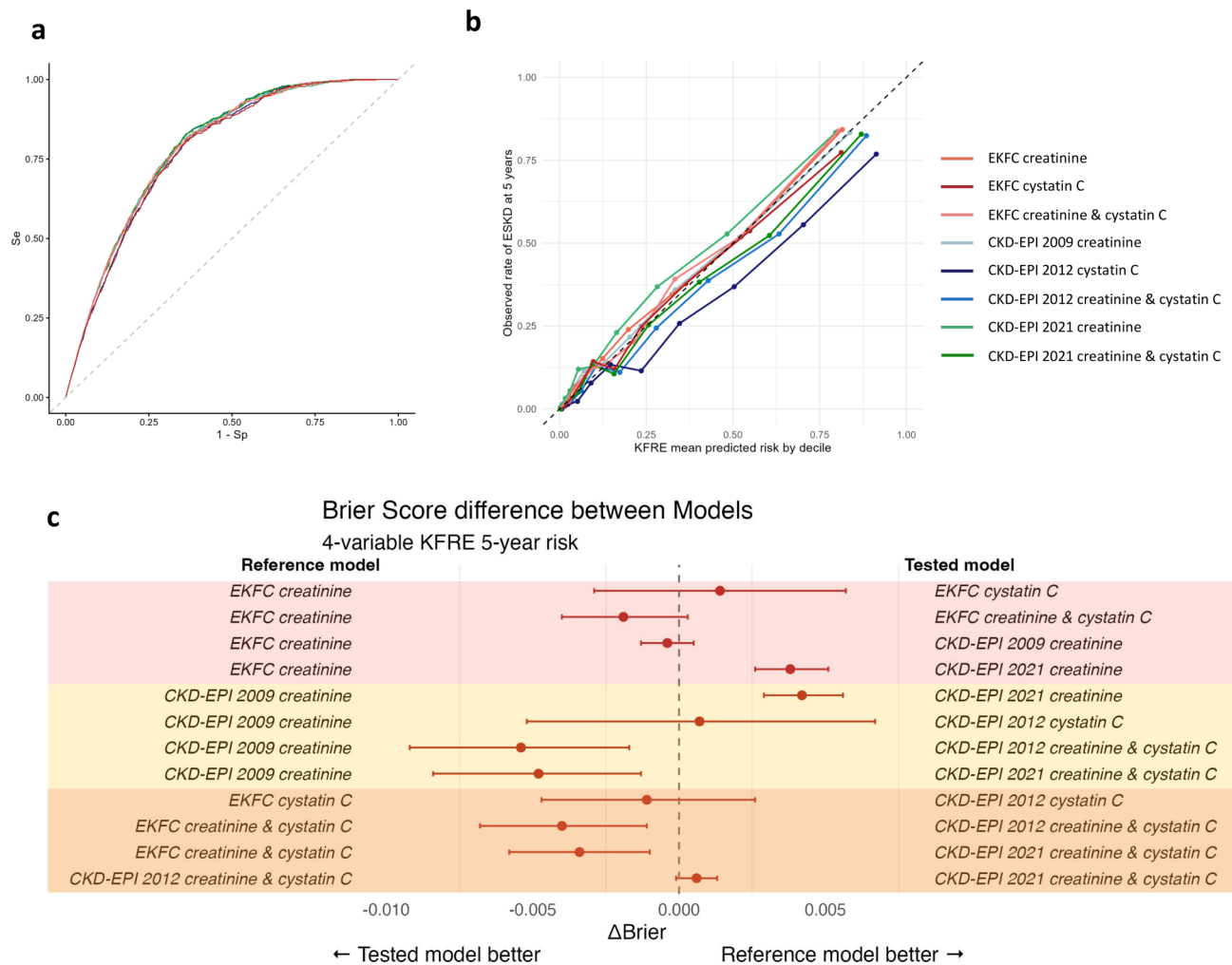


Figure 2: Discrimination and calibration for the four-variable KFRE 5-year risk of kidney failure. (a) ROC curves, (b) calibration curves for the original non-North American scores, and (c) Brier score difference between models.

of underlying eGFR estimator. Our findings confirm that the 5-year KFRE model retains high discriminatory power regardless of the equation used (AUROC > 0.89). However, some nuances emerge when overall predictive performance (in terms of discrimination and calibration) and clinical utility are considered. Beyond discrimination, our study provides novel data regarding the implementation of the KFRE using EKFC equations, which have recently been recommended by KDIGO and EFLM for use in European populations. To our knowledge, this is the first large-scale evaluation of the impact of EKFC equations within the KFRE framework. In addition, by systematically assessing calibration and clinical utility through DCA at guideline-recommended thresholds, our work addresses questions directly relevant to clinical decision-making.

First, we found that the original CKD-EPI 2009 equation, used in the development of KFRE, remains a robust benchmark for 5-year risk prediction. Yet, the EKFC creatinine-based equation performed similarly—if not slightly better—in terms of net benefit at key clinical thresholds (e.g. 40% at 2 years), without loss of discrimination or calibration. These findings are particularly relevant given that EKFC has now been recommended by KDIGO and EFLM for use in White European populations [5, 10].

Second, our results suggest that adding cystatin C, alone or in combination, does not improve the performance of KFRE in predicting kidney failure.

Calibration was not optimal across all versions of KFRE and equations used, in line with previous reports showing non-optimal calibration of KFRE when applied outside North American settings [2, 26]. A recent study showed that the performance of the non-North American four-variable KFRE were improved after recalibration in a Swedish population [27]. Our findings are also consistent with recent data from the French CKD-CAREMEAU study [28], which showed that KFRE calibration was strongly influenced by CKD etiology, while discrimination remains stable.

A high AUROC does not guarantee clinical usefulness, and calibration is essential for determining whether prediction models should inform patient care [29–31]. In our analysis, even models with excellent AUROCs (>0.90) showed calibration curves deviating from the ideal line, underlining that high discrimination does not guarantee reliable individual risk estimation.

The apparent absence of added value for cystatin C is somewhat surprising. These findings should not be interpreted as evidence against cystatin C as a prognostic biomarker per se, but rather as a limitation of applying a creatinine-derived risk

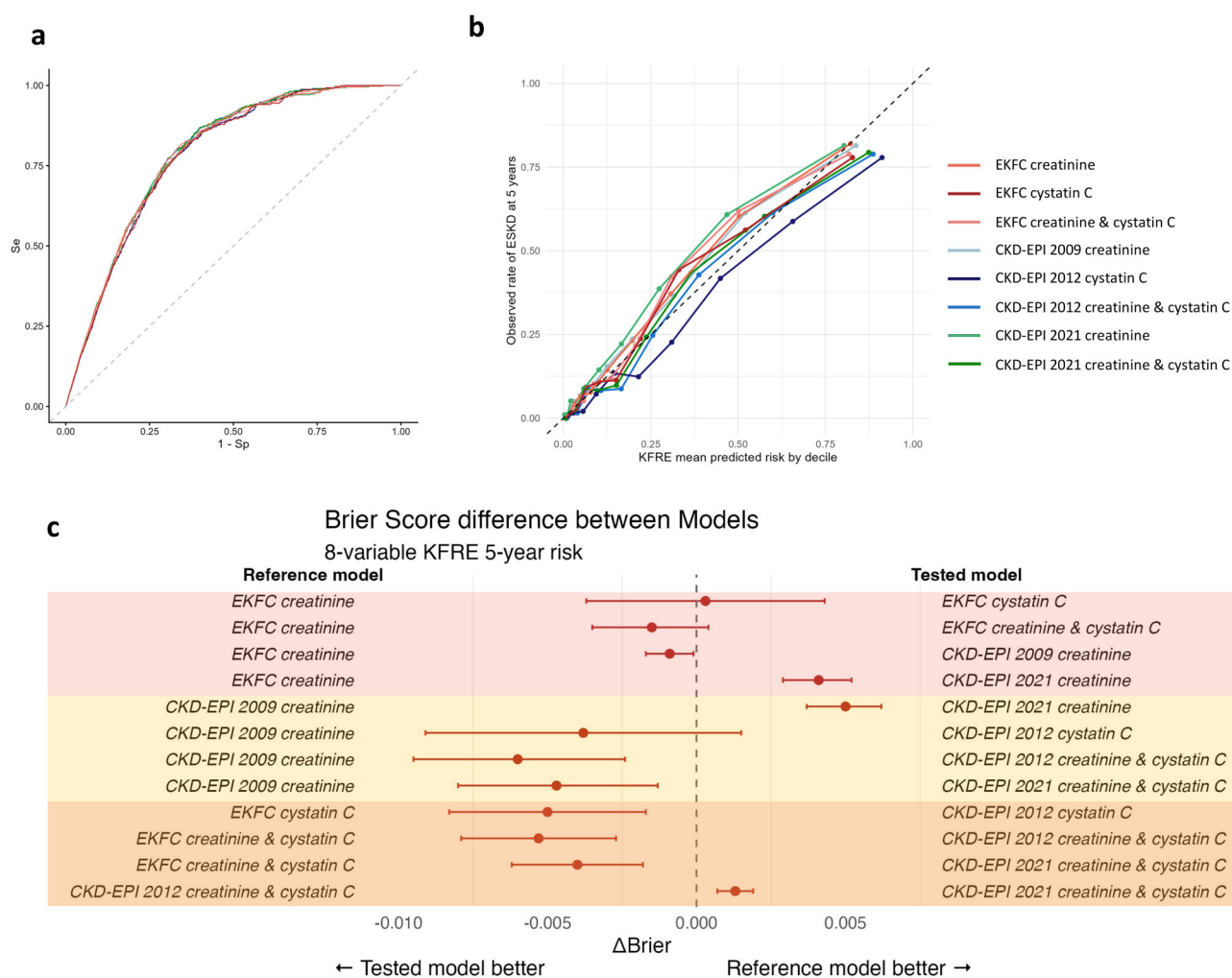


Figure 3: Discrimination and calibration for the eight-variable KFRE 5-year risk of kidney failure. (a) ROC curves and AUROC values, (b) calibration curves for the original non-North American scores, and (c) Brier score difference between models.

equation without model re-derivation. Our study suggests that, for the specific purpose of predicting kidney failure, creatinine alone may be sufficient within the KFRE framework. This observation may reflect the fact that the KFRE was specifically developed and validated to predict progression to kidney failure, whereas cystatin C may capture different aspects of risk, more related to mortality than to renal progression. We observed that the combined creatinine and cystatin C-based CKD-EPI 2012 equation outperformed CKD-EPI 2009 for the 5-year risk prediction. This suggests that the added prognostic value of combining biomarkers may become more apparent over longer prediction horizons. However, this result was not consistent with EKFC equations.

Our findings are consistent with recent large-scale evaluations of the KFRE using the CKD-EPI 2021 creatinine equation. In a multinational analysis of 59 cohorts, Grams et al. showed that replacing creatinine-based CKD-EPI 2009 equations with the 2021 version resulted in minimal changes in discrimination and calibration of the KFRE, without meaningful improvement in overall performance [32]. Similarly, in a contemporary population-based cohort, Atiquzzaman et al. reported only modest shifts in predicted risk following implementation of creatinine-based CKD-EPI 2021 [33].

It should be noted that KFRE was originally developed using the creatinine-based CKD-EPI 2009 equation. Therefore, the overall strong performance of models using this equation is expected. Creatinine-based EKFC showed slightly better clinical utility than CKD-EPI 2009/2012 equations at key thresholds, such as those recommended by KDIGO for dialysis access and transplant planning ($\geq 40\%$ at 2 years) [5]. These findings reinforce recent evidence supporting the use of EKFC equations in European populations, based on clinical utility beyond discrimination and calibration, particularly given the physiological and population-specific normalization approach of the EKFC model, and the absence of race-based adjustments [9, 34].

Our study was conducted in a large, prospective, well-phenotyped national cohort followed over 5 years, with centralized measurements of serum creatinine and cystatin C. We used rigorous statistical methods for assessing both discrimination and calibration of KFRE score evaluated via different eGFR equations, and we proposed decision curves analysis of the different KFRE scores in a French setting of patients with CKD stages G3–G5. However, some limitations should be acknowledged. First, the generalizability of our findings may be limited to French secondary-care populations. Second, a substantial proportion of the original cohort was excluded of the analyses due to missing

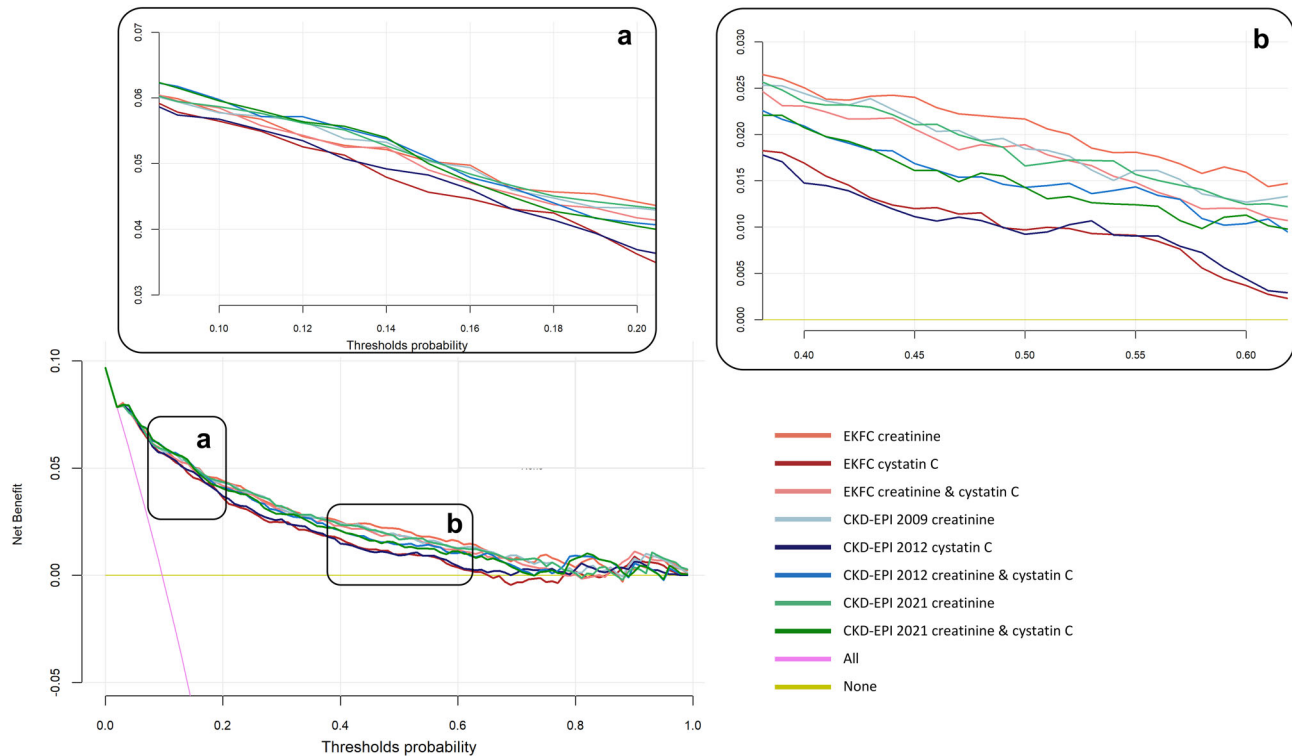


Figure 4: Decision curve analysis for the four-variable KFRE 2-year risk of kidney failure with the different eGFR equations. The “none” line represents the strategy of referring no patient for interventions associated with kidney failure risk, resulting in zero net benefit across all threshold probabilities. The “all” line represents the strategy of referring to all patients, leading to high sensitivity but reduced net benefit at lower thresholds due to unnecessary interventions. KFRE models offer clinical utility when their net benefit curve lies above both the “none” and “all” strategies across relevant risk thresholds.

baseline blood sampling or missing creatinine, cystatin C, or albuminuria measurements. However, the causes of missing cystatin C in CKD-REIN cohort was mostly due to logistic issues, and included and non-included patients did not differ meaningfully in baseline characteristics, suggesting that any selection bias was likely limited (Supplementary Table S4).

In conclusion, our findings highlight that while all KFRE models provided good prognostic discrimination, their performance varied depending on the choice of eGFR equation and biomarker. The creatinine-based CKD-EPI 2009 equation showed consistently strong performance, particularly over shorter time horizons, in line with its original use in the KFRE. However, the EKFC equation—especially when using creatinine alone—emerged as a promising alternative in European populations, offering comparable or improved clinical utility at key decision thresholds. These results support the tailored implementation of KFRE models using creatinine-based CKD-EPI 2009 or EKFC equations in European practice, particularly when aiming to inform timely preparation for kidney replacement therapy.

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AUTHORS' CONTRIBUTIONS

A.L. conceived and designed the study, analyzed and interpreted the data, and drafted the initial draft. P.D. conceived and designed the study, analyzed and interpreted the data, and made critical revisions to the manuscript. M.M. interpreted the data and made critical revisions to the manuscript. A.H. interpreted the data and made critical revisions to the manuscript. N.A.d.P. interpreted the data and made critical revisions to the manuscript. C.M. conceived and designed the study, analyzed and interpreted the data, and made critical revisions to the manuscript. All authors provided important intellectual content and read and approved the manuscript.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Processing of the data supporting the study findings is under the responsibility of the Institut National de la Santé et de la Recherche Médicale (Inserm), France, and complies with the European Regulation (EU) 2016/679 (General Data Protection Regulation) related to "the protection of natural persons with regard to the processing of personal data and rules relating to the free movement of personal data." In compliance with Inserm standard data sharing processes and the agreements obtained from the "Commission nationale de l'informatique et des libertés (CNIL DR-2012-469)" and the ethics committee (IRB00003888 and CCTIRS12.360/CPP), the data can be made available under request to the study coordinating center via ckdrein@inserm.fr. The code used in the analyses is stored within servers at the Centre de recherche en Épidémiologie et Santé des Populations (CESP, Univ Paris-Saclay, Inserm, Villejuif, France) and can also be made available upon request. Any relevant summary statistics for the article are already included within the main article and will be publicly available once the article is published.

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