Risk-based referral model to nephrologist-specialist care in Stockholm

Running head: Clinical utility of KFRE to inform referrals

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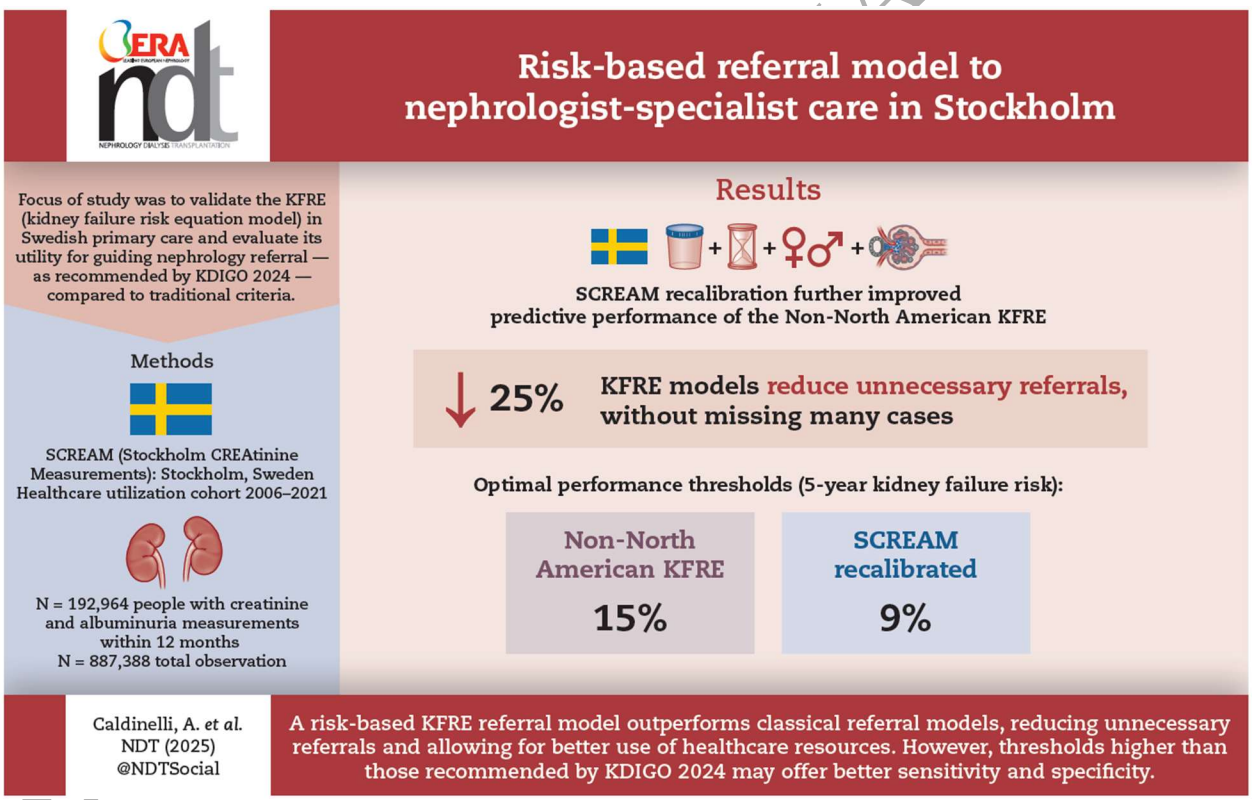
GRAPHICAL ABSTRACT



ABSTRACT

BACKGROUND AND HYPOTHESIS.
For most patients, clinical management of early stages of CKD is performed in primary care settings. KDIGO 2024 guidelines recommended using a 5-year kidney failure risk equation (KFRE) of 3-5% to guide nephrologist referrals. Here, we aimed to assess the impact of adopting–a risk-based referral model compared to traditional referral criteria.

METHODS.
Observational retrospective study of adults with eGFR<60mL/min/1.73m² (Lund-Malmö equation) from the SCREAM project, a healthcare utilization cohort from Stockholm, Sweden. We evaluated the performance of the Non-North American 4-variable KFRE and recalibrated it to better fit our setting. KFRE thresholds were compared with traditional models: the clinical Swedish criteria and the classic KDIGO 2012 criteria, both of which are mainly based on age, eGFR and albuminuria thresholds. Sensitivity, specificity, positive, negative predictive values, reclassification matrices, net reclassification improvement, and decision curve analyses were used to assess performance and clinical utility.

RESULTS.
The study included 887,388 observations from 192,964 individuals. At inclusion, 49% were men, median age was 76 years and median eGFR 54mL/min/1.73m2. During follow-up, 2,624(1.4%) progressed to KRT. KFRE demonstrated a good prediction performance, further improved after recalibration. Both Non-North American and SCREAM recalibrated KFRE provided higher sensitivity and specificity than Swedish and classical KDIGO criteria. KFRE-based referral models yielded better net reclassification improvement, demonstrating superior performance in decision curve analyses. Higher thresholds (15% for the Non-North American KFRE, 9% for the SCREAM recalibrated KFRE) than the KDIGO recommended ones provided the best combined sensitivity and specificity. Compared with traditional referral models, implementation of a risk-based referral would decrease the number of unnecessary referrals by 23% and 25%, respectively.

CONCLUSION.
In a large north-European healthcare system, transitioning to a risk-based referral model would result in an important reduction of unnecessary referrals while maintaining a low rate of missed cases, optimizing resource utilization.

KEY LEARNING POINTS

What was known:

- The 2024 KDIGO guidelines suggest using the KFRE risk model for nephrology referral. Whether a risk-based model outperforms classic referral criteria is not well studied.

This study adds:

- A KFRE-based referral model had better performance compared to classic criteria used in Sweden or those recommended by the previous 2012 KDIGO guidelines.
- The improved performance of the risk-based referral model would be achieved by reducing the number of unnecessary referrals, without missing many cases in which the referral is needed

Potential impact:

- Transitioning to a risk-based referral model would result in an important reduction of unnecessary referrals while maintaining a low rate of missed cases, thus optimizing resource utilization.

Keywords: kidney disease, Kidney Failure Risk Equation, nephrology referral

Introduction

Given the size of the population with chronic kidney disease (CKD) (1) and that, in most cases, progression to kidney failure is slow, early CKD management is often conducted in primary care (2). Referral to nephrologist specialist, in most but not in all cases, is indicated at more severe CKD stages, when loss of kidney function is very rapid, or when CKD complications can no longer be adequately managed in primary care (3, 4).

Clinical guidelines provide diverse opinion-based referral criteria (5), which are usually based on specific thresholds of estimated glomerular filtration rate (eGFR) or albuminuria, and sometimes age. Minor variations in referral criteria can significantly impact referral rates, increasing waiting times and burdening nephrology departments. Many referrals involve individuals at low risk of kidney failure progression, where specialist care may not be necessary (6).

The 2024 KDIGO guidelines recommend using a risk-based referral model with the Kidney Failure Risk Equation (KFRE), indicating to refer patients to nephrologist care when their estimated 5-year kidney failure risk is above 3-5% (7). If health systems are to transition to a risk-based referral model, it is necessary to provide a demonstration of the superiority of this model over more classic referral criteria.

This study aimed to a) validate and, if needed, recalibrate the 4-variable KFRE equation in Swedish primary care settings; b) evaluate KDIGO's suggested thresholds for KFRE; and c) assess the effect of implementing different risk-based thresholds for nephrology referral compared to traditional criteria.

Materials and methods

Data sources and study population

We conducted an observational retrospective study in the Stockholm CREAtinine Measurements (SCREAM) project, a healthcare utilization cohort covering all citizens of the region of Stockholm, Sweden, accessing healthcare during 2006–2021(8). The Swedish unique personal identification number was used to link laboratory data with regional and national administrative databases for complete information on healthcare access, diagnoses and dispensed medications.

Kidney replacement therapy (KRT) data were retrieved from the Swedish Renal Registry (SRR), a nationwide quality registry of patients with CKD referred to nephrologists in Sweden, with >97% coverage of KRT cases (9). The Regional Ethical Review Board in Stockholm approved the study (reference 2017/793-31). The

Swedish National Board of Welfare linked and de-identified the registries, and as the study uses de-identified data, informed consent was not deemed necessary.

Adults (≥18 years) with at least one serum/plasma creatinine and albuminuria test taken on the same date between January 1st, 2006, and December 31st, 2021, were included. Often in clinical practice creatinine and albuminuria are not measured in the same day, so in case the two test were not available on the same day, a window of 12 months was considered, using the latest test date as the index date. We extracted all available pairs of creatinine/albuminuria measurements meeting this condition during the full observation period of a given patient, and thus, when available, we obtained repeated KFRE observations per patient. We excluded patients who, at cohort inclusion (first observation) had eGFR≥60 mL/min/1.73m^2, were undergoing KRT or died within a day. We decided to define CKD based on a single eGFR measurement because it better reflects how KFRE is applied in routine care, where risk is calculated at each creatinine test without requiring confirmation from prior eGFR values (10). The flowchart detailing this process is shown in **Figure S1**.

Study exposure

The study exposures included the 4-variable KFRE, current Swedish criteria for nephrologist referral (11) and the 2012 KDIGO referral criteria (12). We intentionally disregarded referral criteria that are universally applicable regardless of KFRE, eGFR, or ACR, such as rapid kidney disease progression, abnormal urine sediment, acute kidney injury, recurrent nephrolithiasis or the diagnosis of a kidney disease or genetic kidney diseases which require a specific and specialized clinical management. We neither considered persistent CKD abnormalities such as anemia, acidosis or bone disease (7). Although 2024 KDIGO guidelines (7) refer to various validated risk prediction models that could be used at the bedside, we chose to focus on the KFRE for its wide use globally and multiple external validations studies.

The 4-variable KFRE, incorporating age, sex, eGFR and urinary albumin-creatinine ratio (ACR), was developed in patients with CKD stages 3-5 referred to nephrology care in Ontario, Canada (13). External validation in 31 cohorts, including the Swedish Renal Registry, revealed variations in baseline risk, leading to a non-North American recalibration factor for improved accuracy (14). In this study, we used this non-North American recalibrated KFRE equation. eGFR was calculated from serum/plasma creatinine and estimated using the Revised Lund-Malmö (RLM) equation (15) since this is the validated equation automatically reported in Swedish healthcare (11) and the one with highest precision and accuracy against measured GFR in SCREAM (16). We considered ACR tests alongside with urinary Protein to Creatinine Ratio (PCR) tests and dipstick albuminuria tests that were approximated to ACR using the Sumida conversion formula incorporating comorbidities (17).

A description of the referral criteria utilized in this study is presented in Table S1. Briefly, Swedish referral criteria (11) employ fixed thresholds of age, eGFR and albuminuria. The 2012 KDIGO criteria (12) use: eGFR<30 mL/min/1.73m^2, significant albuminuria (ACR ≥300 mg/g) and hypertension refractory to treatment with 4 or more antihypertensive agents. Refractory hypertension was defined in our study as filled prescriptions for 4+ antihypertensive drugs in the 6 months prior to each observation (See definitions in **Table S2**). Filled prescriptions of these medications were ascertained by linkage with the national prescribed drug register (18) which has complete coverage of all dispensed prescriptions at Swedish pharmacies.

Study covariates
History of comorbidities and ongoing medications were defined for descriptive purposes at cohort inclusion. Comorbidities were identified using the full preceding medical history, while medications were considered ongoing if dispensed within six months preceding the index date. Algorithms defining study covariates through clinical diagnostic codes or pharmacy fills are detailed in **Table S2**.

Study outcome
The study outcome was kidney replacement therapy (KRT), defined as the date of start of chronic dialysis or pre-emptive kidney transplantation, within 5 years. During KFRE validation and recalibration of the KFRE we also explored a shorter horizon of 2 years. The date of KRT start was ascertained through linkage with the Swedish Renal Registry(11).

Statistical analysis
Descriptive statistics are represented as medians with interquartile ranges or numbers with percentages.

Model discrimination, calibration and recalibration
If the KFRE was to be automatically reported in electronic healthcare records, it would be calculated every time that albuminuria or creatinine was ordered, and physicians will decide based on reported risks, not considering prior KFRE estimates or changes over. To mimic this clinical practice, and to use data efficiently, we constructed one patient record for each creatinine/albuminuria measure, meeting the conditions above. Each patient record was followed from the creatinine/albuminuria measure until KRT, death or censoring whichever came first. Censoring events were emigration from Stockholm County and end of data collection (31st December 2021). Thus, each patient contributed with multiple patient records. In the development of the original KFRE, death was considered a censoring but not a competing event (13), which results in a systematic overestimation of the risk of KRT by assuming that people can have kidney failure after death (19). To provide more realistic prognostic estimates, we included death as competing risk in the validation process where feasible.

For each record, we calculated the predicted 2- and 5-year KRT risks using the 4-variable KFRE. These predictions were used to evaluate the model's performance in our cohort. Model discrimination was evaluated using cumulative incidence curves, accounting for death as a competing risk, by KFRE levels (14) and using both C-index and Brier score. We assessed calibration by plotting predicted against observed risk to determine if predictions matched actual outcomes. The cohort was divided into ten groups, each representing 10% of the predicted risk distribution. An additional plot was generated for the lowest 20%, as these groups are the most relevant for informing nephrology referral decisions. Observed risk within each group was calculated using a cumulative incidence function, accounting for competing risk. This allowed comparisons of KFRE model predictions with actual KRT incidence in each group.

To improve the model's performance, we recalibrated the 2-year and 5-year KFRE models using a Cox proportional hazards model fitted to our database. In the recalibration process we updated baseline hazard and regression coefficients resulting in the "SCREAM recalibrated KFRE". To retain the original KFRE structure, death was excluded as a competing risk during recalibration. The original model is referred to as the "Non-North American KFRE," while Swedish and KDIGO 2012 criteria are referred together as "traditional referral criteria."

Optimal KFRE thresholds and comparison with classic nephrologist referral models
We compared the prognostic performance of KFRE and traditional referral criteria over a 5-years horizon. Using the Youden index (20), extracted from ROC curves (built including death as competing risk), we

identified optimal thresholds for both KFRE equations based on highest sensitivity and specificity. These optimal thresholds, along with the thresholds of 3% and 5%, were compared against the traditional referral criteria.

For each referral model, we extracted pairs of sensitivity and specificity from the ROC curve. To directly compare the performance across models, we determined the sensitivity of the KFRE models at the threshold corresponding to the specificity of the traditional referral models, and the specificity of the KFRE models at the thresholds corresponding to the sensitivity of the classic referral models. This allowed us to evaluate if the new criteria offered better specificity or sensitivity at equivalent levels.

Model utility

We evaluated the clinical utility of transitioning to a risk-based KFRE model by calculating positive predictive value (PPV, true positives), false positives, negative predictive value (NPV, true negatives), and false negatives for each referral criterion. To assess whether the KFRE model improved risk prediction over traditional criteria, we computed the Net Reclassification Improvement (NRI) (21); incorporating death as competing risk (22). Decision curve analysis (DCA) was used to visually compare the net benefit of referral models across various threshold probabilities (23), also considering death as a competing event.

Sensitivity analyses

We conducted three sensitivity analyses. First, to explore if considered multiple observation per person introduced bias due to test correlation, we repeated analyses using one random observation per patient. Second, to evaluate if approximating dipstick albuminuria to ACR affected KFRE accuracy, we repeated our analyses using a cohort with ACR-only tests. The last sensitivity analysis explored whether there were differences in prognostic performance across time periods. Statistical analyses were performed using R (version 4.3.1). All data have been reported in line with the TRIPOD statement (**Table S15**). We used R software to develop an online calculator for the SCREAM recalibrated model which can be found at this link (SCREAM Recalibrated KFRE Calculator).

Results

Characteristics of the study population

The study included 192,964 adults with eGFR <60 mL/min/1.73m² and concomitant eGFR and ACR tests, contributing 887,388 repeated observations (median 2 [IQR 1–5] per participant). Baseline characteristics are shown in **Table 1**. Median age was 76[IQR 69-82] years, 49% were men, median eGFR was 54[IQR 46-57] mL/min/1.73m^2 and median albuminuria was 21[IQR 16-54] mg/g. Albuminuria was measured with ACR (included converted PCR) in 45% of cases, and the remaining were dipstick tests.

Model discrimination, calibration and recalibration

Among the cohort, 2,624 (1.4%) progressed to KRT and 76,609 (40%) died (Table S3). The 2-year and 5-year non-North American KFRE demonstrated good discrimination, as shown by C-index and Brier score (Table S4) and also by Figure S2. Calibration plots for the 5-year KRT risk predictions are shown in **Figure 1A,** the equivalent plots for the 2-year KRT risk in **Figure S3A**. The 2-year risk model generally showed good calibration but slightly underestimated risk in lower-risk groups and overestimated in higher-risk groups. The 5-year risk model underestimated risk across all groups.

We recalibrated the abovementioned models to better fit the Swedish setting, the derived coefficients of the resulting "SCREAM recalibrated KFRE" are provided in **Appendix 1**. SCREAM recalibrated KFRE models improved calibration, but the 5-year model continued to underestimate risks (**Figure 1B** and **Figure S3B**).

Optimal KFRE thresholds and comparison with classic nephrologist referral models

Optimal 5-year KRT risk thresholds were identified using the ROC curve (**Figure S6**). A threshold of 15% for the Non-North American KFRE and 9% for the SCREAM recalibrated KFRE provided the highest sum of sensitivity and specificity, per the Youden index.

The prediction performance of these thresholds, along with KDIGO's recommended 3% and 5%, were compared to Swedish and classical KDIGO referral models (**Table 2**). All referral models and all KFRE thresholds showed excellent sensitivity (ranging from 0.91 to 0.98). However, specificity varied: classical KDIGO had the lowest specificity (0.63), while the highest specificity was observed at the optimal threshold for the Non-North American KFRE (0.88 at threshold 15%) and for the SCREAM recalibrated KFRE (0.89 at threshold 9%).

Direct comparisons in **Table S5A** show both KFRE models outperform traditional criteria, offering higher sensitivity at equivalent specificity and vice versa. For example, to achieve the same sensitivity as the Swedish referral model (0.98), the threshold of the SCREAM recalibrated KFRE would need to go down to 0.6%. Still, on this threshold, specificity is higher (0.70) than that achieved by the Swedish referral model (0.65, shown in **Table 2**). **Table S5B** directly compares the two KFRE models. At the sensitivity and specificity levels of the 3% and 5% thresholds of the Non-North America KFRE, the SCREAM recalibrated KFRE shows slightly worse performance, with marginally lower specificity at fixed sensitivity and *vice versa*.

Classification performance of the various referral models is shown in **Table 3**. Classic referral models (Swedish and old KDIGO) classify more observations as meeting nephrologist referral criteria, resulting in lower PPVs and higher false positive rates. Conversely, the KFRE models classify fewer observations as eligible for referral, yielding higher PPVs, particularly at the optimal thresholds identified by ROC curve analysis. All models achieved nearly perfect NPVs (~100%) and negligible rates of false negatives (<1%).

Table 4 presents the reclassification matrices comparing Swedish and KDIGO referral models with KFRE at various thresholds. At all thresholds, both KFRE models consistently reclassify as non-eligible for referral many observations incorrectly classified by the Swedish and classic KDIGO criteria.

Model utility

NRI are presented in **Figure 2** and **Table S6**. Both KFRE models improved classification of non-events (NRI-) compared with classic referral models, meaning they are better at identifying patients who do not need referral. However, their performance in classifying events (NRI+) is slightly less accurate, indicating a minor reduction in identifying the absolute numbers of patients who need referrals. Despite this, the overall NRI supports KFRE models. For example, transitioning to a risk-based KFRE referral model using the highest threshold (15% for Non-North American KFRE and 9% for SCREAM recalibrated KFRE), would correctly reclassify 17% of observations of Swedish referral model. This would be mainly achieved by avoiding many "unnecessary" referrals (23-24%), as those patients did not progress to kidney failure within 5 years.

The DCA plot illustrates that KFRE models provide greater net benefit compared to traditional referral criteria across all the threshold probabilities (**Figure 3**).

Sensitivity analyses

By selecting a random observation per individual (n=192,694 individuals), we observe similar results to our main analysis, with KFRE referral models outperforming traditional ones (**Table S8, Figure S7**). Selecting only observations with ACR measurements (n=474,844 observations) provided also similar findings to our main analysis (**Table S11, Figure S8**). The analysis showed consistent results across different time periods (**Table S14**).

Discussion

By exploring kidney failure risk in this large cohort of CKD patients managed in primary healthcare, we provide support for the KDIGO 2024 guidelines recommendation to transition to a risk-based referral model (7). Using KFRE to guide referrals would significantly impact referral patterns and healthcare resource utilization. A risk-based KFRE referral model outperforms current criteria, primarily by reducing unnecessary referrals. However, we also found that using higher KFRE thresholds than those proposed by KDIGO would further improve the models' performance.

In Manitoba Canada, where the KFRE was initially developed, a KFRE risk of >3% over 5 years has been a component of the nephrology referral process over the past years. Compared to the period before the introduction of KFRE, a study observed shorter waiting periods, and thereby improved access to care for patients at the highest risk of CKD progression (24). In the UK, two studies in primary care found KFRE thresholds >5 % (25) or >3% (26) superior to the UK National Institute for Health and Care Excellence (NICE) criteria (27). As a result, NICE changed their recommendations to encourage implementing a risk-based referral model in the UK (28). Similar prognostic superiority of KFRE>3% compared with Australian referral criteria was observed in a small study of 1511 patients under nephrology care (29).

Our study expands preceding evidence with novel observations and methodological improvements. We evaluate the prognostic performance across the entire KFRE risk spectrum. A key finding is the reporting of optimal KFRE thresholds, which were markedly higher than those suggested by guidelines. The rationale for most studies and guidelines referring to 3% and 5% thresholds is unclear, but it seems to derive from physician surveys (14) and the original KFRE study (13), conducted in a relatively small cohort of people already referred to nephrologist care with CKD stages 3b-5, does not fully represent the population managed in primary care, in whom CKD stage 3a is more prevalent and less likely to progress to KRT within 5 years. Our findings thus show that higher KFRE thresholds naturally improve performance. Our study also benefits from utilizing repeated observations within a unified healthcare system, reducing the impact of fragmented care or unequal care access. Finally, we considered the competing risk of death during the validation process and considered all repeated measurements per individual to better approximate real-world scenario.

Since this study was conducted in Sweden, we compared KFRE performance against current Swedish referral criteria. To generalize to a more general setting in other countries we also compared KFRE with common referral criteria based on eGFR, albuminuria, and refractory hypertension, widely used in national guidelines (5). Regardless of the model compared, KFRE offered improved prognostication.

We demonstrate that transitioning to a risk-based referral model would importantly reduce the number of referrals by eliminating false positives, with the reductions in efforts, time and costs that this conveys. Translating to numbers, using the non-north American optimal KFRE threshold of 15% instead of the Swedish referral criteria would decrease the proportion of referrals in Stockholm region from 37% to 15%. Such reduction in consultation volume is expected to decrease waiting times for high-risk patients, thereby allowing for better use of healthcare resources (24). This would however not be desirable if many patients progressing to kidney failure were missed. In our study, we however show that using a higher KFRE threshold also increased the number of true positives (from 11% using the Swedish criteria to 27% with the optimal KFRE) with minimal impact on the false negatives, which were only 0.3% higher with the optimal KFRE referral model.

We recognize that our prognostic prediction cannot prove the real effect of its implementation. The underlying assumption for referral to nephrologist care is that patients who present late to specialty care have worse outcomes compared to patients who have a timely referral. This being said, the well-intended belief of a benefit of early vs late referral has not been proven in the form of a clinical trial, and most observational studies on this topic have focused on patients at a very high risk of end stage kidney disease (ESKD), where the late presenters have been known to the nephrology department for <3 months before starting KRT (30). Qualitative research (31) suggests that patients with advanced CKD desire to have prognostic information and are interested in knowing their risk of developing ESKD, and patients believe (32) that the use of KFRE in clinical decision making would be beneficial for them.

We believe that our results can assist European policy makers in general, and Swedish ones in particular, in their decision to adopt the suggestions by KDIGO guidelines and transition to a risk-based referral model (7). For Sweden, we propose a recalibrated KFRE equation that could be integrated in the automatic reporting of eGFR currently available in most electronic health data systems. We then suggest adopting a KFRE referral threshold of 9%, demonstrating the best prognostic value in the Swedish setting. For other non-North American settings, we propose an optimal KFRE threshold of 15%. However, we encourage individual countries and health systems to investigate the best-fitting equations and thresholds tailored to their background risk.

Our study has limitations. Since our proposed thresholds were derived and tested on the same dataset the results may not generalize to other regions or periods, though supporting literature strengthens their potential applicability (25, 26, 29). Implicit in the calculation of KFRE, we could not evaluate the utility of this model in patients with an eGFR of ≥60 mL/min/1.73m^2. However, the 5-year risk of KRT in such patients is likely low, except perhaps for young patients with nephrotic range proteinuria, which is *per se* an indication for referral to nephrology care. Moreover, numerous studies report low rates of ACR testing in people at risk of CKD, where guidelines emphasize annual screening. This continues to represent a barrier towards identification of patients in need of timely referral (33). It is also important to notice that although risk-based referral models may have benefits, they do not replace educational programs directed to primary health care, since there are circumstances when nephrology referral should be based on other grounds than risk.

In conclusion, transitioning from traditional criteria to a risk-based model for referrals to nephrologist care would substantially reduce the number of referrals, while improving the identification of patients at highest risk of KRT. Our findings thus support the recommendations from the 2024 KDIGO guidelines, and have significant implications for patients, clinicians, policy makers, and resource allocators.

Data availability statement

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data may be shared on reasonable request for academic research collaborations that fulfill GDPR as well as national and institutional ethics regulations and standards by contacting Juan-Jesus Carrero Juan-Jesus Carrero (juan.jesus.carrero@ki.se).

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Authors' contributions

The study was designed by J.J.C., M.E., A.C. and A.L.F.; Data were acquired by J.J.C.; Statistical analyses was carried out by A.C. with support from A.S.; Interpretation was done by A.C., A.S., A.L.F., J.J.C., and M.E.; The draft of the manuscript was written by A.C. and J.J.C.; Revision of the final version of the manuscript was done by all authors.

Conflict of interest statement

The authors do not report any direct disclosure in relation to this study. Unrelated to the study, J.J.C. reports funding to Karolinska Institutet by AstraZeneca, Astellas, Amgen, Vifor Pharma, and NovoNordisk; personal honoraria for lectures by Fresenius Kabi, Baxter Healthcare, and Abbott, and being a member of advisory boards for Astellas, AstraZeneca, and GSK. ME reports funding from AstraZeneca and Astellas pharma, advisory boards from Astellas, and payment for lectures by AstraZeneca, Astellas, Boehringer-Ingelheim, and Vifor Pharma.

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Table 1: Descriptive characteristics at cohort inclusion (unique individuals) and of all multiple observations

	Patients, at cohort inclusion N = 192,964	Multiple observations N = 887,388
Baseline characteristics		
Age, years	76 (69, 82)	77 (69, 83)
Male, n (%)	93,788 (49%)	446,980 (50%)
eGFR (mL/min/1.73 m^2)	54 (46, 57)	47 (34, 55)
Albuminuria (mg/g)	21.5 (15.6, 53.9)	27.9 (16.9, 133.1)
Type of albuminuria test		
Dipstick	106,706 (55%)	412,544 (46%)
uACR	86,258 (45%)	474,844 (54%)
Comorbidities		
Hypertension	114,550 (59%)	609,002 (69%)
Diabetes	34,279 (18%)	276,137 (31%)
Any cardiovascular disease	61,918 (32%)	360,448 (40%)
Coronary artery disease	25,922 (13%)	156,602 (18%)
Cerebrovascular disease	16,757 (9%)	97,313 (11%)
Peripheral artery disease	6,518 (3%)	45,008 (5%)
Heart failure	19,202 (10%)	133,201 (15%)
Drugs		
Any antihypertensive agents	147,831 (77%)	753,170 (85%)
>3 antihypertensive agents	25,827 (13%)	170,224 (19%)

Continuous data expressed as median (interquartile range) and categorical as number (percentage).
Abbreviations: CKD, Chronic Kidney Disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; KRT, kidney replacement treatment; uACR, urinary albumin-to-creatinine ratio.

Table 2: Sensitivity and specificity of nephrologist-referral models for prediction of 5-year KRT risk

	KFRE referral model				Traditional criteria			
	Non-North American KFRE		SCREAM recalibrated KFRE		Swedish referral model		Classic KDIGO referral model	
Threshold	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
3%	0.98	0.72	0.95	0.82	0.98	0.65	0.98	0.63
5%	0.97	0.78	0.93	0.86				
9% (*)	-	-	0.91	0.89				
15% (*)	0.91	0.88	-	-				

** Optimal threshold according to Youden Index*
Abbreviations: KDIGO, Kidney Disease Improving Global Outcome; KFRE, Kidney Failure Risk Equation; SCREAM, Stockholm CREAtinine Measurements.

Table 3: Classification performance of different nephrologist-referral models for predicting the 5-year risk of KRT.

	Observations eligible for referral			Observations non-eligible for referral		
Referral model	**Number of observations (proportion)**	**True positives (PPV)**	**False positives**	**Number of observations (proportion)**	**True negatives (NPV)**	**False negatives**
Swedish referral model	328 039 (37%)	36 939 (11%)	291 100 (89%)	559 349 (63%)	558 647 (99.9%)	702 (0.1%)
Classic KDIGO referral model	347 112 (39%)	36 835 (11%)	310 277 (89%)	540 276 (61%)	539 470 (99.9%)	806 (0.1%)
KFRE referral model						
• **Non-North American KFRE**						
KFRE 3%	270 136 (30%)	36 950 (14%)	233 186 (86%)	617 252 (70%)	616 561 (99.9%)	691 (0.1%)
KFRE 5%	219 313 (25%)	36 565 (17%)	182 748 (83%)	668 075 (75 %)	666 999 (99.9%)	1 076 (0.2%)
KFRE 15% (optimal*)	130 654 (15%)	34 640 (27%)	96 014 (73%)	756 734 (85%)	753 733 (99.9%)	3 001 (0.4%)
• **SCREAM recalibrated KFRE**						
KFRE 3%	182 978 (21%)	35 970 (20%)	147 008 (80%)	704 410 (79%)	702 739 (99.9%)	1 671 (0.2%)
KFRE 5%	153 683 (17 %)	35 391 (23%)	118 292 (77%)	733 705 (83%)	731 455 (99.9%)	2 250 (0.3%)
KFRE 9% (optimal *)	122 395 (14%)	34 348 (28%)	88 047 (72%)	764 993 (86%)	761 700 (99.9%)	3 293 (0.4%)

** Optimal threshold according to Youden Index*
Abbreviations: KDIGO, Kidney Disease Improving Global Outcome; KFRE, Kidney Failure Risk Equation; NPV, negative predicted value; PPV, positive predicted value; SCREAM, Stockholm CREAtinine Measurements.

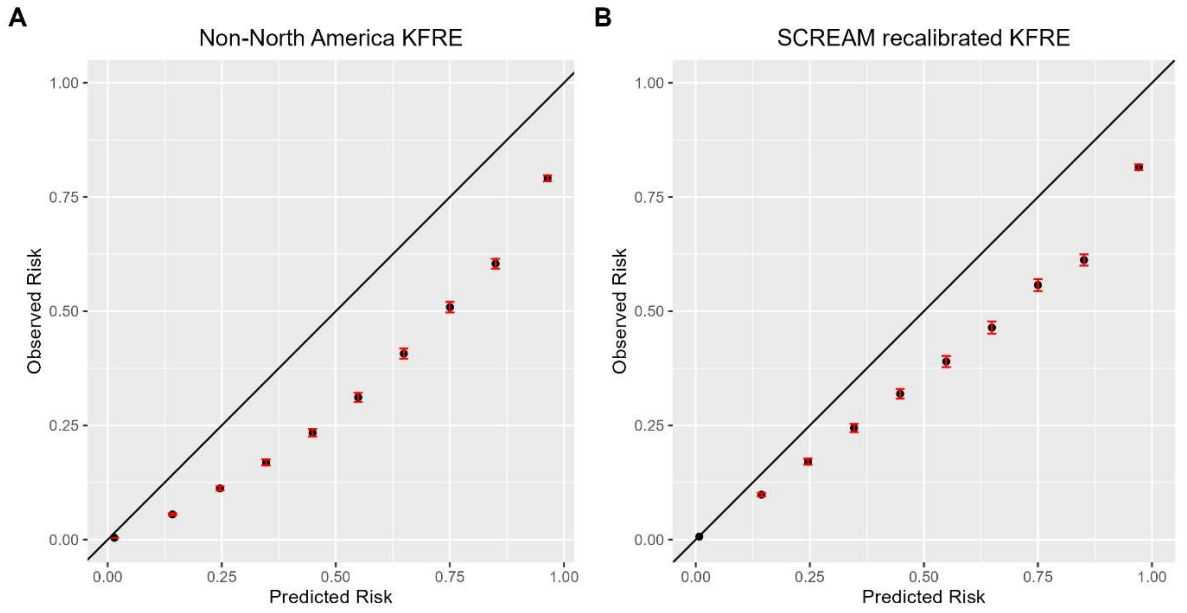
Table 4: Reclassification performance of the KFRE referral model (panel A non-north American KFRE, Panel B SCREAM recalibrated KFRE) versus the Swedish and classic KDIGO referral models in the prediction of 5-year risk of KRT.

Panel A. Non-North American KFRE referral model							
	KFRE 3%		**KFRE 5%**		**KFRE 15% (optimal *)**		
	No referral	*Referral*	*No referral*	*Referral*	*No referral*	*Referral*	*Total*
Swedish referral model							
No referral	506 741 (57%)	52 608 (6%)	526 584 (59%)	32 765 (4%)	554 538 (62%)	4 811 (0.5%)	559 349 (63%)
Referral	110 511 (13%)	217 528 (24%)	141 491 (16%)	186 548 (21%)	202 196 (23%)	125 843 (14%)	328 039 (37%)
Total	617 252 (70%)	270 136 (30%)	668 075 (75%)	219 313 (25%)	756 734 (85%)	130 654 (15%)	
Classic KDIGO referral model							
No referral	502 525 (57%)	37 751 (4%)	524 992 (59%)	15 284 (2%)	539 543 (61%)	733 (0.001%)	540 276 (61%)
Referral	114 727 (13%)	232 385 (26%)	143 083 (16%)	204 029 (23%)	217 191 (24%)	129 921 (15%)	347 112 (39%)
Total	617 252 (70%)	270 136 (30%)	668 075 (75%)	219 313 (25%)	756 734 (85%)	130 654 (15%)	
Panel B. SCREAM recalibrated referral model							
	KFRE 3%		**KFRE 5%**		**KFRE 9% (optimal *)**		
	No referral	*Referral*	*No referral*	*Referral*	*No referral*	*Referral*	*Total*
Swedish referral model							
No referral	535 032 (60%)	24 317 (3%)	545 097 (61%)	14 252 (2%)	554 352 (62%)	4 997 (0.6%)	559 349 (63%)
Referral	169 378 (19%)	158 661 (18%)	188 608 (22%)	139 431 (15%)	210 641 (24%)	117 398 (13%)	328 039 (37%)
Total	704 410 (79%)	182 978 (21%)	733 705 (83%)	153 683 (17%)	764 993 (86%)	122 395 (14%)	
Classic KDIGO referral model							
No referral	534 599 (60%)	5 677 (1%)	538 168 (61%)	2 108 (0.002%)	539 657 (61%)	619 (0.001%)	540 276 (61%)
Referral	169 811 (19%)	177 301 (20%)	195 537 (22%)	151 575 (17%)	225 336 (25%)	121 776 (14%)	347 112 (39%)
Total	704 410 (79%)	182 978 (21%)	733 705 (83%)	153 683 (17%)	764 993 (86%)	122 395 (14%)	

** Optimal threshold according to Youden Index*

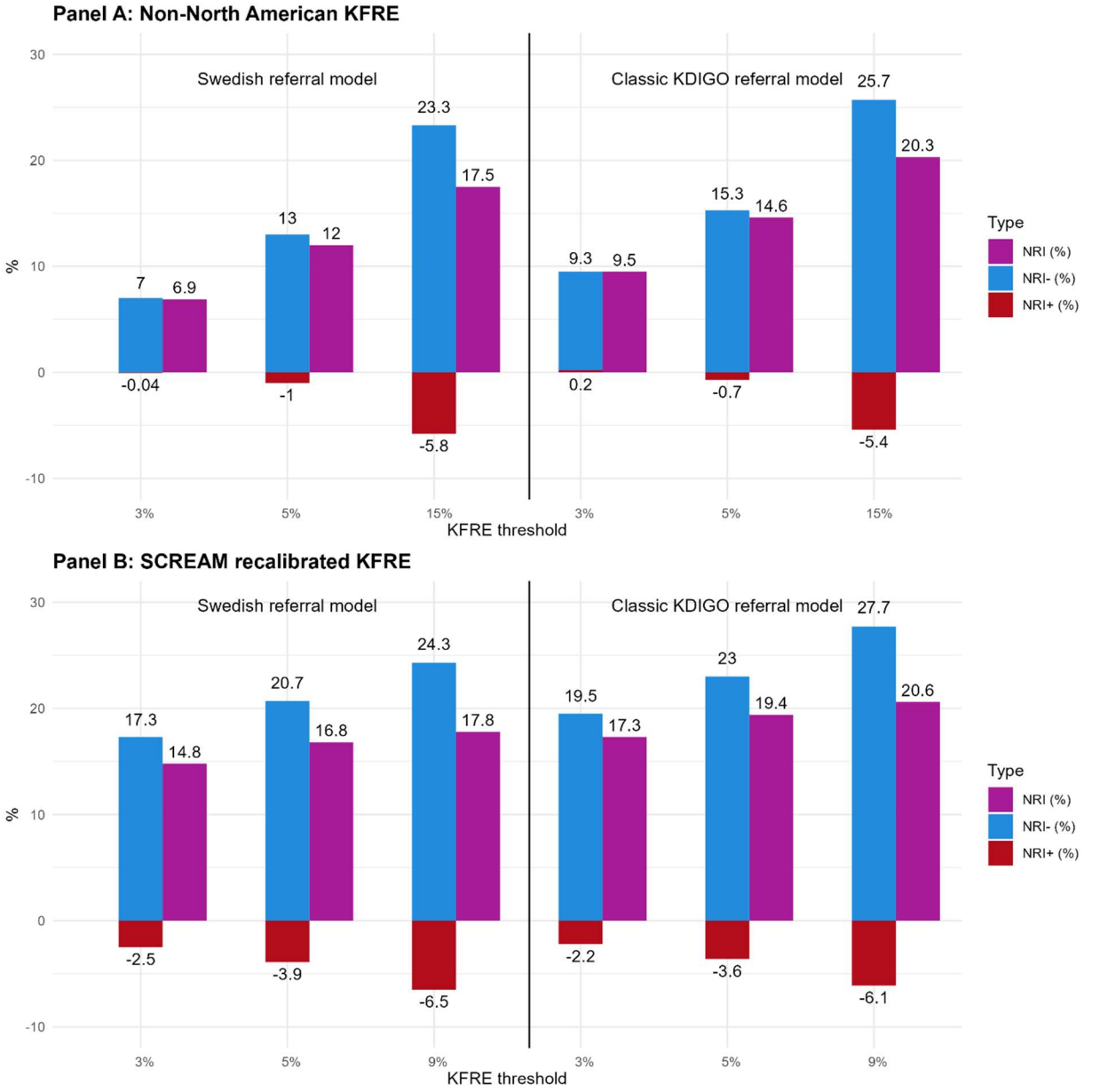
Abbreviations: KDIGO, Kidney Disease Improving Global Outcome; KFRE, Kidney Failure Risk Equation; SCREAM, Stockholm CREAtinine Measurements.

Figure 1: Calibration plot of expected versus observed 5-year KRT risk of the non-North America calibrated KFRE (panel A) and the SCREAM recalibrated KFRE (panel B)



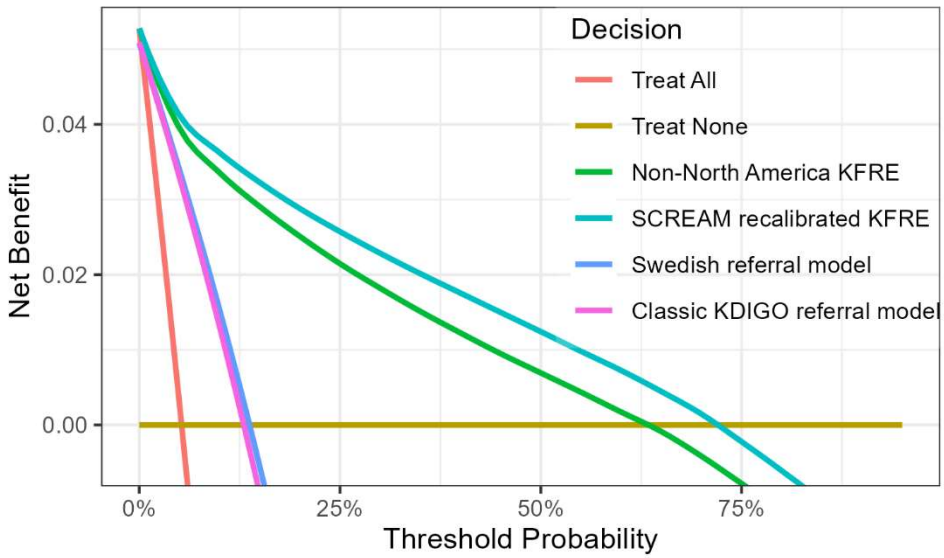
Groups are split into 10% of predicted risk. The black dots represent the predicted and observed risk for each group. The red vertical lines represent the 95% CIs. The black line indicates perfect calibration.
Abbreviations: KFRE, Kidney Failure Risk Equation; SCREAM, Stockholm CREAtinine Measurements.

Figure 2: Net Reclassification Improvement (NRI) for selected thresholds of KFRE compared with the Swedish and Classic KDIGO nephrologist referral models in the prediction of 5-year risk of KRT.



Panel A shows NRI with the Non-North American KFRE and Panel B shows NRI with the SCREAM Recalibrated KFRE. Abbreviations: KDIGO, Kidney Disease Improving Global Outcome; KFRE, Kidney Failure Risk Equation; NRI; Net Reclassification Index; NRI+; Net Reclassification Index for events; NRI-; Net Reclassification Index for non-events; SCREAM, Stockholm CREAtinine Measurements.

Figure 3: Decision curve analyses comparing differences in net benefit across different nephrologist-referral models for predicting the 5-year risk of KRT.



Threshold probabilities refer to the point at which a clinician would opt for treatment; so lower thresholds represent the clinical setting where the clinician is more concerned about missing true positives and therefore is willing to act even if the probability of the outcome is low. While high threshold probabilities mean that the clinician is more concerned about avoiding false positives and so clinician will only act when there is a high probability of the outcome.

Abbreviations: KDIGO, Kidney Disease Improving Global Outcome; KFRE, Kidney Failure Risk Equation; SCREAM, Stockholm CREAtinine Measurements.