BMC Nephrology

RESEARCH Open Access

External validation, recalibration, and clinical utility of the kidney failure risk equation in patients with advanced CKD: a nationwide retrospective cohort analysis in Peru

Jessica Ivonne Bravo-Zúñiga[1†], Percy Soto-Becerra[2*†], Edgar Juan Coila-Paricahua[3], Ricardo Chávez-Gómez[1], Eduardo Pérez-Tejada[4], Anselma Victoria Pardo-Villafranca[4], Lizbeth Carmen Arce-Gallo[4] and Daysi Diaz-Obregón[5]

Abstract

Background The Kidney Failure Risk Equation (KFRE) is widely used for predicting kidney failure, but its external validity in Latin America is limited. A previous study in Peru found that KFRE was miscalibrated but did not evaluate its recalibration or clinical utility.

Methods We conducted a retrospective cohort study using data from EsSalud's Renal Health Surveillance Program (2013–2022), including 30,031 patients with chronic kidney disease (CKD) stages G3-4. Kidney failure was defined by dialysis initiation or nephrologist-confirmed end-stage renal disease. Calibration was assessed using observed-to-expected (O/E) ratios and differences, calibration slope, and intercept, while discrimination was evaluated using the concordance index (C-index). Recalibrated models were developed, and decision curve analysis (DCA) was performed to evaluate clinical utility.

Results The original KFRE demonstrated good discrimination (C-index: 0.88 at 2 years, 0.85 at 5 years) but poor calibration in-the-large: O/E ratios indicated mean underestimation of risk at 2 years (O/E ratio: 1.84) and a slight mean overestimation at 5 years (O/E ratio: 1.06). Original KFRE also had poor weak (slope: 0.58) and poor moderate calibration. Recalibrated models improved calibration in-the-large, but none achieved good weak (all slope < 1) and moderate calibration. However, DCA showed a higher net benefit for KFRE-based nephrology referrals (in original and recalibrated by method D) compared to Peruvian and international guidelines, especially over a 5-year horizon.

Conclusions Despite miscalibration, KFRE remains valuable for guiding nephrology referrals in Peru, with recalibrated models offering potential improvements. This is the first study in Latin America to rigorously assess the clinical utility of KFRE.

†Jessica Ivonne Bravo-Zúñiga and Percy Soto-Becerra contributed equally to this work.

*Correspondence:
Percy Soto-Becerra
percy.soto@upn.edu.pe

Full list of author information is available at the end of the article

Clinical trial number Not applicable. This study is not a clinical trial.

Keywords Chronic kidney disease, Kidney failure risk equation, External validation, Clinical utility, Peru, Decision curve analysis

Background

Chronic kidney disease (CKD) is a growing global health challenge, affecting about 10% of the population and often leading to kidney failure, requiring costly interventions like dialysis or transplantation [1, 2]. Recent guidelines, including NICE 2021 and KDIGO 2024 [3, 4], emphasize that accurate, individualized risk prediction models can help reduce the burden of CKD by identifying high-risk patients who may benefit from early interventions. This enables healthcare providers to make informed decisions about when to refer patients to nephrology, allowing for the implementation of nephroprotective strategies to slow disease progression and facilitating timely planning for renal replacement therapy (RRT), ultimately improving patient outcomes and optimizing healthcare resources.

While international guidelines recommend the use of the Kidney Failure Risk Equation (KFRE) for predicting kidney failure [3, 4]its implementation in Peru remains limited [5, 6]. The Peruvian Clinical Practice Guideline instead relies on a combination of estimated glomerular filtration rate (eGFR) and albuminuria for nephrology referrals, similar to the earlier approach of NICE 2014 guidelines [7]. Despite endorsements from the Latin American Nephrology Society to recommend KFRE [8] concerns have persisted due to the lack of region-specific evidence supporting its utility. This highlights the importance of externally validating prognostic models like KFRE within the specific settings where they are intended to be used [9–11]particularly in the Peruvian and broader Latin American context.

Although KFRE has shown strong prognostic performance in international contexts [12–28]recent studies have identified miscalibration in various countries [16, 17, 19, 22, 23, 29, 30]. In Peru, a recent study found KFRE to perform well in a cohort from Lima, the country's capital and largest urban center, but did not undertake recalibration, raising questions about its nationwide applicability [31]. Moreover, region-specific evidence in Latin America is scarce, with no studies evaluating the clinical utility of KFRE [32, 33]. Addressing this gap is essential to provide evidence that supports the use of KFRE in the Peruvian context and informs tailored CKD management strategies. Therefore, this study aims to perform an external validation and recalibration of the KFRE to predict kidney failure, as well as assess its clinical utility in guiding decisions for referral and planning for RRT in a nationwide cohort of patients with CKD stages G3-4 in Peru.

Methods

Study design, population and data source

We conducted a retrospective cohort study following the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines [11, 34] to externally validate, recalibrate and assess the clinical utility of the KFRE model for predicting the risk of kidney failure at 2-year and 5-year horizons in patients diagnosed with chronic kidney disease (CKD) stages 3–4 (eGFR > 15 and < 60 ml/min per 1.73 m^2) between 2013 and 2022 across all 45 care networks of EsSalud (see TRIPOD checklist in online Supplementary Material). The data were collected and managed by the National Renal Health Center as part of the national renal health surveillance system (VISARE, by its Spanish acronym). For health centers within the Rebagliati Network, the largest in Lima, data were directly sourced from the UMERC informatics application designed specifically for this network to provide information to VISARE, as previously described [31]. Additionally, data from the Kaelin Hospital were provided directly by the hospital itself due to its special status as a public-private partnership, which maintains its own renal health surveillance and does not routinely report to the CNSR.

Validation model and predictors

We validated the 4-variable KFRE, which includes age (scaled to 10 years), eGFR (ml/min per 1.73 m^2 using the CKD-EPI formula), sex, and urinary albumin/creatinine ratio (ACR) in mg/g [25]. Standardized laboratory protocols were followed across health facilities to measure these predictors (see Supplementary Methods for details on KFRE equations, coding of predictors, CKD-EPI formula and laboratory considerations).

Outcome variable

The primary outcome was the time to kidney failure, defined as the date of the first hemodialysis or peritoneal dialysis based on administrative data from the National Center for Renal Health or through specific ICD-10 diagnoses (e.g., N18.5, N18.6, Z99.2, Z49.1, Z49.2, Z94.0). This computational phenotyping approach has been validated in previous studies and is further detailed in the Supplementary Methods. Death was considered a competing risk, with mortality data obtained from both the National Death System of Peru and the National Registry of Identification and Civil Status, which together cover more than 90% of all deaths in the country. For more

information on the outcome definitions and data sources, please refer to the supplementary material.

Follow-up time

Patients were followed until kidney failure, death or the administrative censorship date (December 31, 2022), whichever occurred first. Censoring occurred at loss to follow-up or study end.

Sample size

Due to the comprehensive nature of the national dataset, a specific sample size calculation was unnecessary. All patients meeting inclusion criteria were analyzed (see Fig. 1 and Table S4). Since the number of events per EsSalud health network was significantly low—often fewer than 100 events, and in many instances, nearly zero—it was decided to evaluate the performance of KFRE across the entire country without considering regions as separate clusters.

Statistical analysis

Initial data analyses were performed to identify extreme values, inconsistencies, and missing data. Winsorization of albumin-creatinine ratio (ACR) values at the 1.5th and 98.5th percentiles was conducted [35]. Missing data were managed using multiple imputation via Additive Regression, Bootstrapping, and Predictive Mean Matching, creating 100 imputed datasets [36]. To ensure that the imputation model was congenial (at least semicompatible) with the competing risk models used in the substantive analysis, interactions between all predictors and the cumulative baseline hazards for kidney failure and death were included in the imputation process [37]. This step aimed to improve the accuracy of the imputations and their compatibility with the intended analyses (see Supplementary Methods for a detailed description).

For the external validation of the KFRE, model discrimination was assessed using the concordance index (C-index) at 2 and 5 years. In line with the TRIPOD guidelines, model performance was evaluated through both discrimination and calibration assessments, incorporating the consideration of competing risks based on recent methodological recommendations [11]. Calibration was evaluated through assessment of calibration in-the-large: observed-to-expected (O/E) ratios, difference and calibration intercepts; weak calibration: slopes calibration; and moderate calibration via calibration plots. All these measures were obtained accounting for competing risk [38, 39]. The calibration curves were obtained using LOESS smoothing applied to the cumulative baseline hazard predicted by the Fine-Gray model

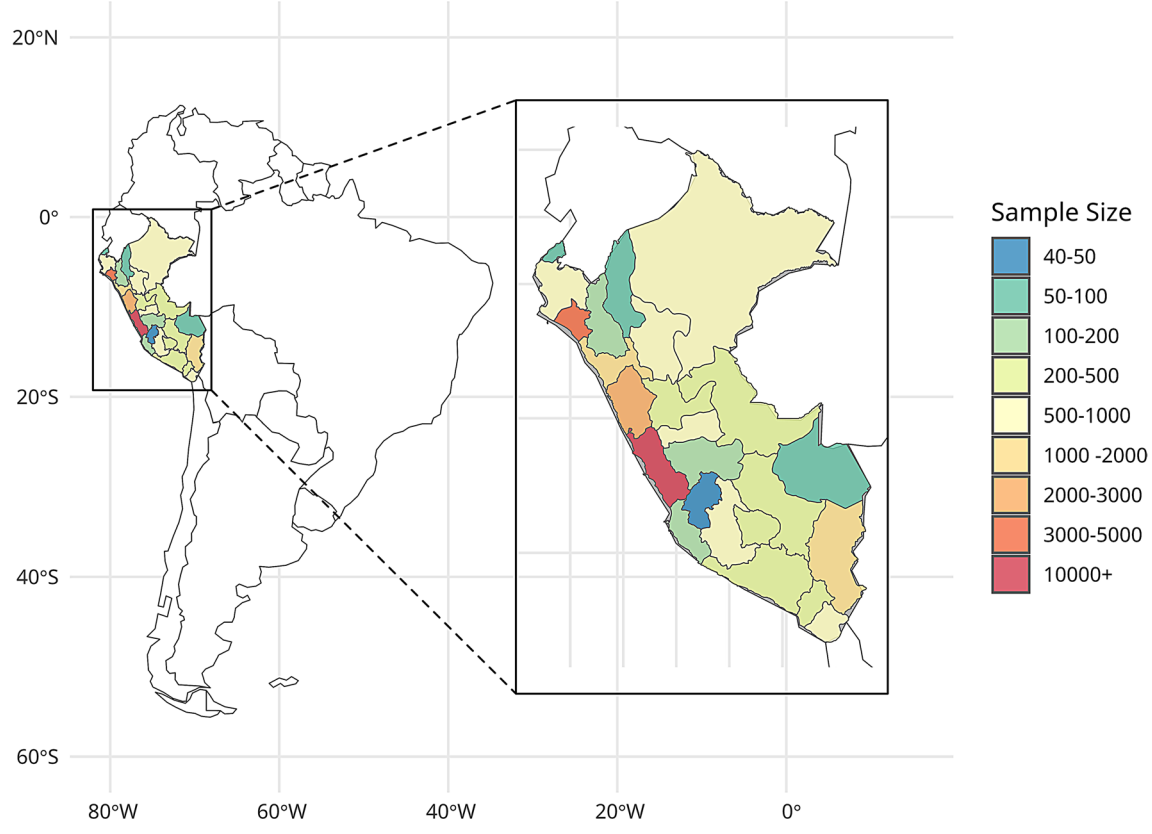

Fig. 1 Regional distribution from EsSalud's patients included in the analysis at national level

for subdistribution hazards [38, 39]. See Supplementary Methods for further details.

Recalibration was performed using four methods [35]: Methods A and B used the traditional Cox model without accounting for competing risks, as originally proposed in the KFRE model by Tangri et al. [25]. Method A adjusted baseline risk only, while Method B adjusted both baseline risk and the magnitude of the linear predictor. Methods C and D, in contrast, employed the Cause-Specific Cox model to account for competing risks. Method C adjusted the baseline risk, and Method D combined baseline risk adjustment with linear predictor adjustment while considering competing risks.

Clinical utility was assessed using decision curve analysis [40] by comparing the net benefit of the original and recalibrated KFRE models against the Peruvian National Guidelines [5, 6] and NICE 2014 Guidelines for nephrology referral [7]. For each prediction horizon (2 and 5 years), we evaluated the utility of using KFRE to guide decisions for referral and planning for renal replacement therapy. Predefined reasonable decision thresholds (based on existing literature) were used to identify patients who might benefit from referral. For long-term management and nephroprotection to halt or reverse CKD progression, a 5-year horizon was used, with thresholds typically ranging between 3–5%[5,6]. For planning renal replacement therapy, the 2-year horizon was considered, with decision thresholds set at higher probabilities, usually around 20–40%[5,6].

The final estimates and standard errors were pooled across the imputed datasets using Rubin's rules, and 95% confidence intervals were calculated based on these standard errors [41]. All statistical analyses were performed using R version 4.3. The reproducible code used for this analysis is available in an open GitHub repository (https://github.com/psotob91/kfre-ckd-nationwide-essalud-peru).

Language editing assistance The authors utilized ChatGPT-4o, a Large Language Model (LLM) developed by OpenAI, to review and improve the English grammar and style of this manuscript. The AI tool was employed solely for language editing purposes and was not used to generate or create any content.

Results

Study population

Out of 152,084 patients screened between January 1, 2013, and December 30, 2022, in all EsSalud facilities nationwide under the VISARE program, 30,031 met the selection criteria for CKD stages G3-4 (Fig. 2). Only 38.4% (11,540) had complete data for the four variables required for KFRE estimation. After multiple imputations, all eligible individuals were included in the analysis.

Table 1 summarizes the key sociodemographic and clinical characteristics of the study population after imputation. Of the total, 56.4% were women, and ages ranged from 18 to 109 years, with a median age of 73.8 years. The prevalence of diabetes mellitus (41.5%) and hypertension (75.8%) was high, with most participants classified as stage G3a (61.6%) or G3b (27.3%). A detailed comparison of population characteristics with and without imputation is provided and according to outcome are showed in Table S5 and S6, respectively.

Cumulative incidences of kidney failure at 2 and 5 years were 2.73% (95% CI: 2.55%-2.92%) and 4.76% (95% CI: 4.51%-5.02%), respectively (Table S2). The cumulative incidences of death without kidney failure were notably higher, with values of 6.96% (95% CI: 6.67%-7.26%) at 2 years and 19.71% (95% CI: 19.22%-20.2%) at 5 years. The detailed cumulative incidence curve for both kidney failure and death are shown in Fig. 3. 2-year and 5-year KFRE's predicted risk is shown in Figure S1. The distribution of four KFRE equation variables is shown in Figure S2.

Predictive performance of the original 4-variable KFRE equation

KFRE showed good discrimination across all time horizons, with C-indices of 0.88 (95% CI: 0.86–0.89) at 2 years and 0.85 (95% CI: 0.84–0.87) at 5 years (Table 2). However, calibration was poor across all time horizons.

At 2 years, the model underestimated the risk of kidney failure, as indicated by an observed-to-expected (O/E) ratio of 1.84 (95% CI: 1.7–1.99). Although the calibration intercept was not statistically different from zero (0.02, 95% CI: -0.13 to 0.18), the pronounced O/E ratio suggests that the model underestimates the actual risk on average. At 5 years, the O/E ratio was closer to 1 at 1.06 (95% CI: 1 to 1.13), which might initially suggest an alignment between predicted and observed risks. However, the calibration intercept was significantly negative (-0.47, 95% CI: -0.59 to -0.35), reinforcing the presence of systematic underestimation of the mean risk.

In both time horizons, the calibration slope was below 1 (0.58 for both 2 and 5 years), indicating overly extreme predictions — underestimating risks for low-risk individuals and overestimating for high-risk individuals. Calibration curves in Fig. 4 further illustrate these trends. Overall, these results highlight that KFRE has poor mean, weak and moderate calibration in Peruvian population of EsSalud.

Recalibration of the KFRE model

Recalibration was performed using four methods (A-D). Recalibrated equations has shown in Table 3.

As shown in Table 4, Method D had the best calibration-in-the-large at both 2 and 5 years, with O/E ratios

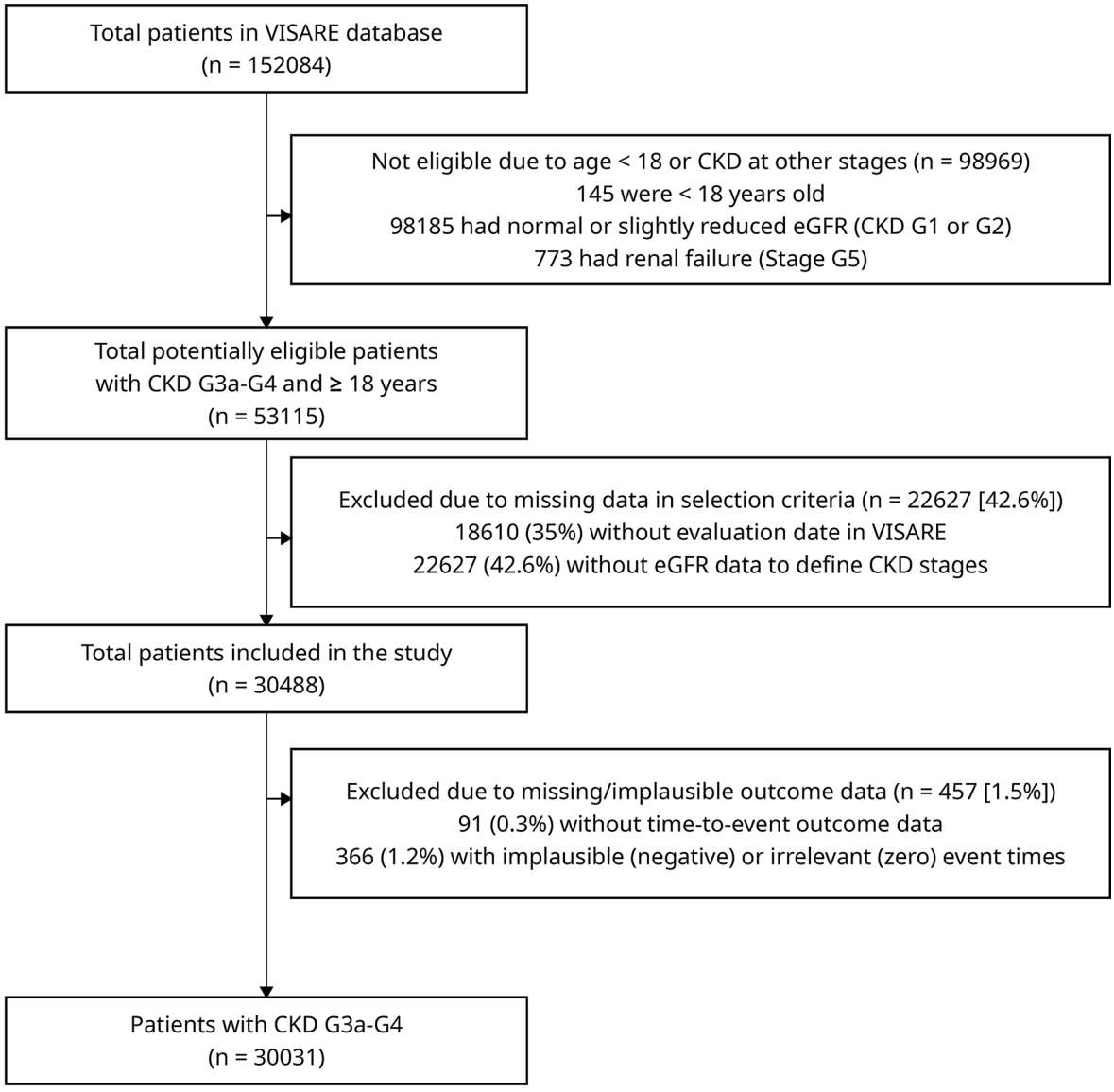

Fig. 2 Flowchart of study participant inclusion

close to 1 (1.02 at 2 years; 1.04 at 5 years) and calibration intercepts not significantly different from zero. Despite this, the calibration slope (0.81 for both time horizons) indicates some underestimation in low-risk individuals and overestimation in high-risk ones, failing in achieve good weak calibration.

The calibration plots for Method D show a reasonable alignment with the ideal 45-degree line, with minor overestimation at higher risk levels (Fig. 5). It's important to note that this overestimation at the upper tail involves fewer data points, which may impact the curve's stability. In contrast, Methods A, B, and C show more pronounced deviations, especially at the extremes. Thus, while Method D is not perfectly calibrated, it offers the most balanced performance among the recalibrated models.

Clinical utility of original model KFRE and recalibrated versions

Figure 6 presents the decision curve analysis comparing the net benefits of the original and recalibrated KFRE models across 2-year and 5-year horizons. Method D demonstrated the highest net benefit across most thresholds; however, the difference was modest compared to the original KFRE model. For example, at a 5% threshold over 5 years, Method D had a net benefit of 0.0261, nearly identical to the original model's 0.0255.

All models, including the original KFRE and its recalibrated versions, outperformed alternative referral strategies based on the NICE 2014 guidelines and Peruvian National Guidelines across a range of thresholds. This suggests that the KFRE models, despite calibration issues, effectively balance harm and benefit by accurately

Table 1 Baseline characteristics (at first recorded evaluation in VISARE) of patients with CKD G3-4 included in the analysis

Characteristic	*N* = 30,031
Sex	
Female	13,097 (43.6%)
Male	16,934 (56.4%)
Age (years)	
Mean (SD)	73.8 (11.1)
Median (Q1 - Q3)	75.0 (67.0–82.0)
Min - Max	18.0–109.0
EsSalud Network	
Metropolitan Lima	14,784 (49.2%)
Other Regions	15,247 (50.8%)
Hypertension	
No	7,254 (24.2%)
Yes	22,777 (75.8%)
Diabetes Mellitus	
No	17,567 (58.5%)
Yes	12,464 (41.5%)
Persistent Albuminuria Categories	
A1	14, (48.8%)
A2	10,095 (33.6%)
A3	5,274 (17.6%)
eGFR Categories	
G3a	18,491 (61.6%)
G3b	8,201 (27.3%)
G4	3,339 (11.1%)
CKD KDIGO Classification	
Low risk	0 (0.0%)
Moderately increased risk	9,403 (31.3%)
High risk	10,169 (33.9%)
Very high risk	10,459 (34.8%)
Serum Creatinine (mg/dL)	
Mean (SD)	1.4 (0.4)
Median (Q1 - Q3)	1.3 (1.2–1.6)
Min - Max	0.9–4.5
eGFR using CKD-EPI (ml/min/1.73 m^2)	
Mean (SD)	45.9 (10.8)
Median (Q1 - Q3)	48.5 (39.4–54.5)
Min - Max	15.0–60.0
Albumin-Creatinine Ratio (mg/g)	
Mean (SD)	802.1 (3,534.1)
Median (Q1 - Q3)	32.0 (8.1–160.3)
Min - Max	0.6–27,817.5
Urine Albumin (mg/dl)	
Mean (SD)	35.8 (161.5)
Median (Q1 - Q3)	1.6 (0.4–8.4)
Min - Max	0.0–1,365.2
Urine Creatinine (mg/dL)	
Mean (SD)	60.8 (50.5)
Median (Q1 - Q3)	49.2 (27.0–85.0)
Min - Max	0.1–221.3
Death at 2 years*	
No	27,640 (92.0%)
Yes	2,391 (8.0%)
Outcomes at 2 years	
Alive w/o Kidney Failure	27,227 (90.7%)
Kidney Failure	793 (2.6%)
Death w/o Kidney Failure	2,011 (6.7%)
Death at 5 years*	
No	24,261 (80.8%)
Yes	5,770 (19.2%)
Outcomes at 5 years	
Alive w/o Kidney Failure	23,579 (78.5%)
Kidney Failure	1,308 (4.4%)
Death w/o Kidney Failure	5,144 (17.1%)

*Death after o before kidney failure

SD: standard deviation, IQR: first quartile and third quartile, ACR, urine albumin to creatinine ratio; CKD, chronic kidney disease; eGFR, glomerular filtration rate estimated by CKD Epidemiology Collaboration formula

identifying more patients for referral while minimizing unnecessary ones.

At the 2-year horizon, the net benefit of both the original KFRE and the recalibrated models was slightly superior to the "refer none" strategy at threshold probabilities of 20% and 30%. For instance, at a 20% threshold over 2 years, Method D had a net benefit of 0.0016, while the original model had a net benefit of 0.0015. However, at higher threshold probabilities (> 40%), the net benefit of these models became lower than the "refer none" strategy, indicating limited utility in these scenarios.

In summary, Methods D and B showed the highest clinical utility, consistently demonstrating the highest net benefits at both 2- and 5-year horizons. However, these differences were relatively small, indicating that the original KFRE model remains a viable option for clinical decision-making.

Sensitivity analysis

A sensitivity analysis was performed without applying winsorization to the extreme values of the ACR. Figure S3 and S4 show the distribution of KFRE's predicted risks and four variables, respectively in the original dataset without winsorization of ACR. The results remained similar to the primary analysis (Table S9, Figures S5, S6 and S7), indicating that the winsorization of ACR values did not significantly impact the predictive performance or calibration of the KFRE model.

Discussion

Main findings

This study externally validated the KFRE multivariable model in a national cohort of EsSalud patients with CKD stages 3–4, recalibrated KFRE for this population, and assessed the clinical utility of the original and recalibrated versions. While KFRE showed strong discrimination for predicting kidney failure at both 2 and 5 years,

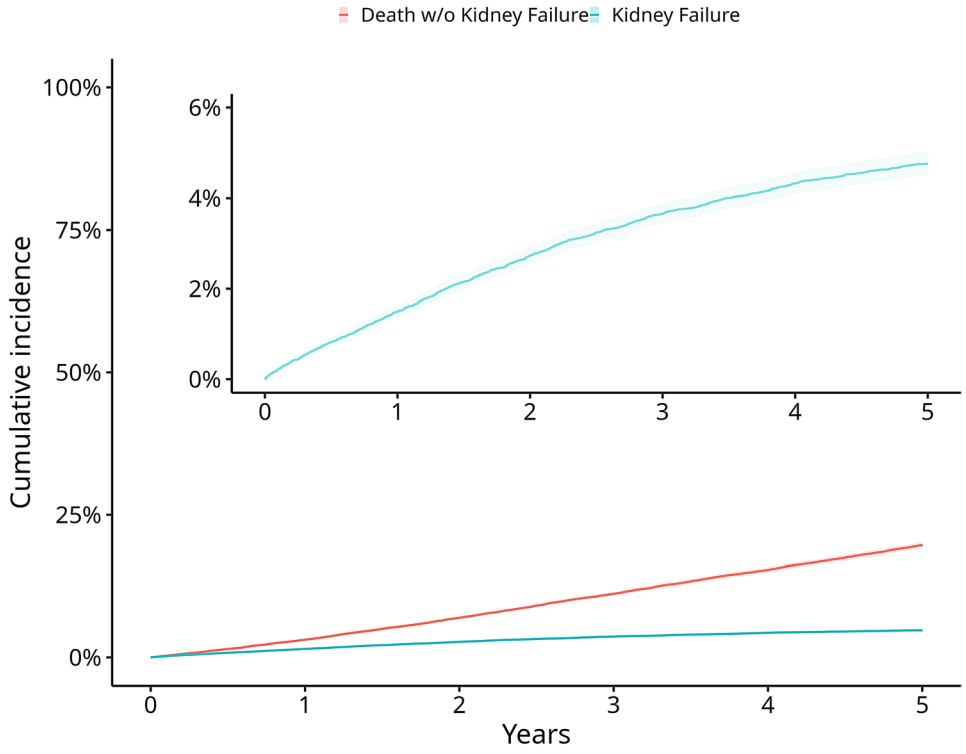

Fig. 3 Cumulative incidence function curves for Kidney Failure and Death in patients with CKD G3-4 included in the study

Table 2 External validation metrics for predictive performance of the original 4-Variable KFRE model

Validation aspect and performance measure	Time horizon	
	t = 2 years	t = 5 years
Calibration		
Average predicted risk	1.48%	4.48%
Average observed risk (95% CI)	2.73% (2.54–2.92%)	4.76% (4.51–5.02%)
O/E ratio (95% CI)	1.84 (1.7 to 1.99)	1.06 (1 to 1.13)
O-E difference (95% CI)	1.25% (1.05–1.44%)	0.29% (0–0.58%)
Calibration intercept (95% CI)	0.02 (-0.13 to 0.18)	-0.47 (-0.59 to -0.35)
Calibration slope (95% CI)	0.58 (0.53 to 0.63)	0.58 (0.54 to 0.62)
Discrimination		
C-index up to t years (95% CI)	0.88 (0.86 to 0.89)	0.85 (0.84 to 0.87)

%, percentage; C-index, truncated agreement index; CKD, chronic kidney disease; O/E and O-E, observed vs. expected ratio and differences, respectively; t, time

it exhibited poor calibration. Two recalibrated models (Methods B and D) improved calibration-in-the-large, yet all recalibrated models struggled with weak or moderate calibration. The recalibrated models maintained a similar pattern to the original KFRE, overestimating risk for high-risk individuals and underestimating it for low-risk individuals.

Despite these calibration issues, the original and recalibrated KFRE versions offered a net benefit compared to the strategy of referring no patients. Their net benefit also surpassed that of the Peruvian National Guidelines and NICE 2014 guidelines across various thresholds. Thus, while the original KFRE and its recalibrated versions may not perfectly predict individual risk, they remain useful tools for guiding nephrology referrals in Peru.

When assessing early referral for renal replacement therapy preparation, the net benefit of KFRE at 2 years turned negative at higher thresholds, indicating that unnecessary referrals (false positives) may outweigh correct ones (true positives). However, for decisions involving long-term referral at 5 years, the KFRE models showed a positive net benefit across thresholds of 3–10%, indicating their utility in effectively identifying high-risk patients who would benefit from early nephrology intervention.

Comparison with previous literature

The 4-variable KFRE model has been externally validated in over 30 countries across all continents [42]: North America [12–15, 43–46]Europe [16–18]Asia [19–23] Oceania [24, 30]and more recently, Latin America [31–33]. However, apart from the cohorts from Chile and Brazil in the 1990s used to recalibrate the initial KFRE model and derive a specific equation for non-North American countries [25]evidence on external validity in

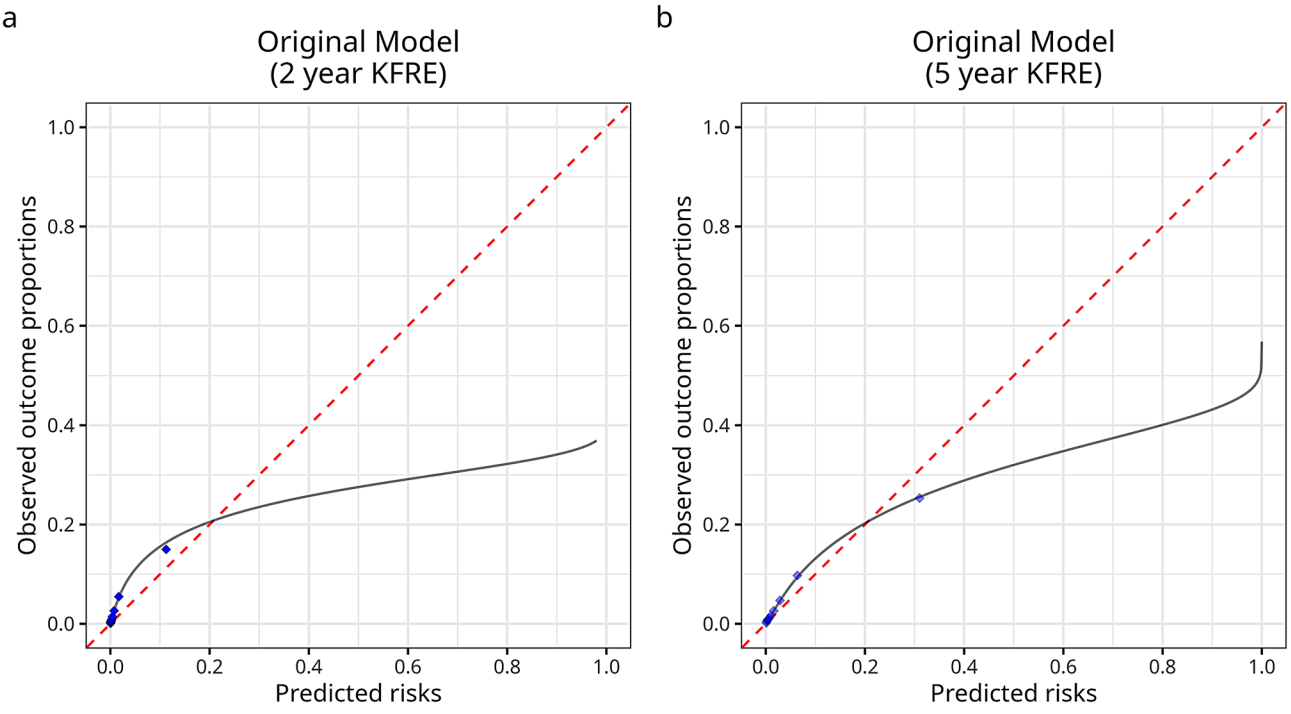

Fig. 4 Calibration curves of the original KFRE model. The predicted risk by the KFRE model is shown on the x-axis, and the observed risk on the y-axis. The observed risk was estimated using cumulative incidence function curves to account for the competing risk of death without kidney failure. CKD: chronic kidney disease

Latin America was absent for nearly two decades. Previous research in Peru showed KFRE's good discrimination but highlighted poor calibration, a finding we confirmed in a larger national cohort [31]. Other studies in Latin America, such as those in Colombia and Uruguay, reported good discrimination and calibration but lacked adequate validation methodologies, limiting the comparability of their results with our findings [32, 33]. These methodological issues underscore the urgent need to generate high-quality evidence on the applicability of KFRE in clinical practice in Latin America, ensuring that well-sound methods are used to properly validate prognostic models.

In contrast, the literature from non-North American regions, excluding Latin America, is more extensive. Globally, studies consistently demonstrate KFRE's high discrimination (>0.80)[12–28], but have identified moderate calibration issues, particularly with overprediction in high-risk groups. Differences in predictor profiles and incidence rates do not fully account for the poor calibration observed in Peru. For example, the renal failure incidence rate in our study closely matches that of the original model (see Table S8). However, our population's characteristics, including higher albuminuria levels, higher diabetes prevalence, and exclusion of G5 stages, may contribute to the observed miscalibration.

Importantly, our decision to exclude stage G5 patients is well supported by both the intended clinical use of the KFRE model and prevailing practices in the literature. The KFRE is primarily designed for use in outpatient settings where earlier stages of CKD (G3–4) are managed, and its application in stage G5 is inherently less useful, as these patients are already recognized as high risk and often follow different management pathways (e.g., conservative or palliative care). Notably, Tangri's original derivation and validation cohorts included a very low proportion of G5 patients (approximately 5.3%) [25], and several subsequent external validation studies have similarly focused on patients with CKD stages G3–4 [27, 47]. This selective validation approach is common, valid, and reasonable, as it ensures that the model's calibration and performance are most relevant to the population where it is intended to be applied [34, 35, 48].

It is also important to note that although one might argue that the exclusion of stage G5 patients could explain part of the miscalibration, evidence from studies such as Ramspek et al. [16] indicates that calibration issues persist even when G5 patients are included. Ramspek et al. [16] attribute these issues not solely to the inclusion of patients with advanced CKD, but to a combination of factors—including heterogeneity in clinical profiles and the failure to account for the competing risk of death. In fact, Tangri's original model did not account for this competing risk, leading to an overprediction of renal failure risk in settings where the incidence of death is high [25]. In our population, incidence of pre-dialysis

Table 3 Original and recalibrated equations

Time horizon	Equations
Original model	
2 years	$1-0.9832^{e^{(-0.2201\times\left(\frac{age}{10}-7.036\right)+0.2467\times(sex-0.5642)-0.5567\times\left(\frac{eGFR}{5}-7.222\right)+0.4510\times(\log(ACR)-5.137))}}$
5 years	$1-0.9365^{e^{(-0.2201\times\left(\frac{age}{10}-7.036\right)+0.2467\times(sex-0.5642)-0.5567\times\left(\frac{eGFR}{5}-7.222\right)+0.4510\times(\log(ACR)-5.137))}}$
Method A: Baseline risk adjustment without considering competing risk	
2 years	$1-0.9688^{e^{(-0.2201\times\left(\frac{age}{10}-7.036\right)+0.2467\times(sex-0.5642)-0.5567\times\left(\frac{eGFR}{5}-7.222\right)+0.4510\times(\log(ACR)-5.137))}}$
5 years	$1-0.9363^{e^{(-0.2201\times\left(\frac{age}{10}-7.036\right)+0.2467\times(sex-0.5642)-0.5567\times\left(\frac{eGFR}{5}-7.222\right)+0.4510\times(\log(ACR)-5.137))}}$
Method B: Baseline risk adjustment + adjustment of linear predictor magnitude without considering competing risk	
2 years	$1-0.9550^{e^{0.7126042\times(-0.2201\times\left(\frac{age}{10}-7.036\right)+0.2467\times(sex-0.5642)-0.5567\times\left(\frac{eGFR}{5}-7.222\right)+0.4510\times(\log(ACR)-5.137))}}$
5 years	$1-0.9130^{e^{0.7126042\times(-0.2201\times\left(\frac{age}{10}-7.036\right)+0.2467\times(sex-0.5642)-0.5567\times\left(\frac{eGFR}{5}-7.222\right)+0.4510\times(\log(ACR)-5.137))}}$
Method C: Baseline risk adjustment considering competing risk	
2 years	$1-0.9699^{e^{(-0.2201\times\left(\frac{age}{10}-7.036\right)+0.2467\times(sex-0.5642)-0.5567\times\left(\frac{eGFR}{5}-7.222\right)+0.4510\times(\log(ACR)-5.137))}}$
5 years	$1-0.9425^{e^{(-0.2201\times\left(\frac{age}{10}-7.036\right)+0.2467\times(sex-0.5642)-0.5567\times\left(\frac{eGFR}{5}-7.222\right)+0.4510\times(\log(ACR)-5.137))}}$
Method D: Baseline risk adjustment + adjustment of linear predictor magnitude considering competing risk	
2 years	$1-0.9572^{e^{0.7126042\times(-0.2201\times\left(\frac{age}{10}-7.036\right)+0.2467\times(sex-0.5642)-0.5567\times\left(\frac{eGFR}{5}-7.222\right)+0.4510\times(\log(ACR)-5.137))}}$
5 years	$1-0.9240^{e^{0.7126042\times(-0.2201\times\left(\frac{age}{10}-7.036\right)+0.2467\times(sex-0.5642)-0.5567\times\left(\frac{eGFR}{5}-7.222\right)+0.4510\times(\log(ACR)-5.137))}}$

eGFR, estimated glomerular filtration rate; urine albumin/creatinine ratio (ACR)

Table 4 Validation metrics for predictive performance of recalibrated KFRE models

Validation aspect and performance measure	Method A[1]	Method B[2]	Method C[3]	Method D[4]
t = 2 years				
Calibration				
Average predicted risk	2.52%	2.82%	2.45%	2.69%
Average observed risk (95% CI)	2.73% (2.54–2.92%)	2.73% (2.54–2.92%)	2.73% (2.54–2.92%)	2.73% (2.54–2.92%)
O/E ratio (95% CI)	1.08 (1.01 to 1.16)	0.97 (0.9 to 1.04)	1.11 (1.04 to 1.19)	1.02 (0.95 to 1.09)
O-E difference (95% CI)	0.21% (0.02–0.4%)	-0.09% (-0.28–0.1%)	0.28% (0.09–0.47%)	0.04% (-0.15–0.23%)
Calibration intercept (95% CI)	-0.6 (-0.74 to -0.46)	-0.1 (-0.2 to 0)	-0.57 (-0.71 to -0.42)	-0.05 (-0.15 to 0.05)
Calibration slope (95% CI)	0.58 (0.53 to 0.63)	0.82 (0.75 to 0.88)	0.58 (0.53 to 0.63)	0.82 (0.75 to 0.88)
Discrimination				
C-index up to t years (95% CI)	0.88 (0.86 to 0.89)	0.88 (0.86 to 0.89)	0.88 (0.86 to 0.89)	0.88 (0.86 to 0.89)
t = 5 years				
Calibration				
Average predicted risk	4.48%	5.19%	4.14%	4.59%
Average observed risk (95% CI)	4.76% (4.51–5.02%)	4.76% (4.51–5.02%)	4.76% (4.51–5.02%)	4.76% (4.51–5.02%)
O/E ratio (95% CI)	1.06 (1.01 to 1.12)	0.92 (0.87 to 0.97)	1.15 (1.09 to 1.22)	1.04 (0.98 to 1.1)
O-E difference (95% CI)	0.28% (0.02–0.54%)	-0.42% (-0.68% to -0.17%)	0.62% (0.37–0.88%)	0.18% (-0.08–0.43%)
Calibration intercept (95% CI)	-0.47 (-0.57 to -0.37)	-0.16 (-0.23 to -0.08)	-0.36 (-0.47 to -0.26)	-0.02 (-0.09 to 0.06)
Calibration slope (95% CI)	0.58 (0.54 to 0.62)	0.81 (0.76 to 0.86)	0.58 (0.54 to 0.62)	0.81 (0.76 to 0.86)
Discrimination				
C-index up to t years (95% CI)	0.85 (0.84 to 0.87)	0.85 (0.84 to 0.87)	0.85 (0.84 to 0.87)	0.85 (0.84 to 0.87)

%, percentage; C-index, truncated agreement index; CKD, chronic kidney disease; O/E and O-E, observed vs. expected ratio and differences, respectively; time, time

[1]Method A: Baseline risk adjustment without considering competing risk

[2]Method B: Baseline risk adjustment + adjustment of linear predictor magnitude without considering competing risk

[3]Method C: Baseline risk adjustment considering competing risk

[4]Method D: Baseline risk adjustment + adjustment of linear predictor magnitude considering competing risk

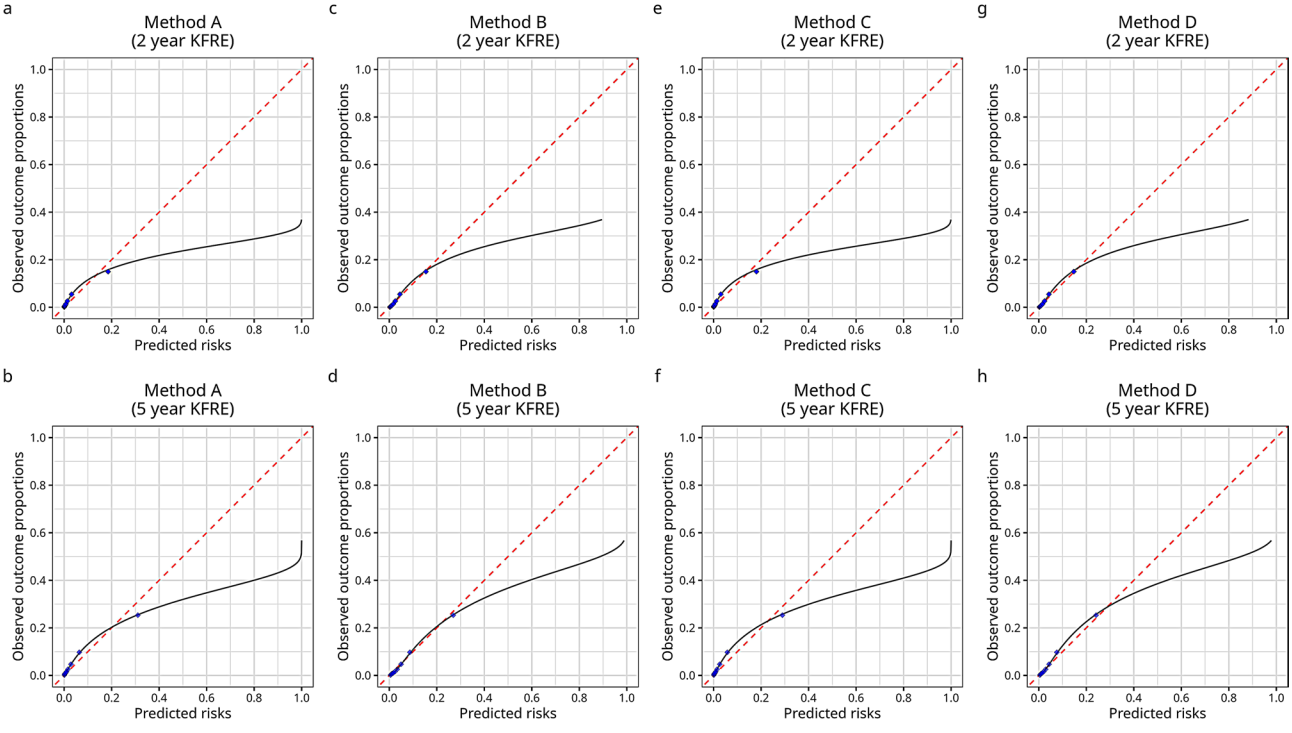

Fig. 5 Calibration plots for the recalibrated KFRE models showing observed outcome proportions against predicted risks. Recalibrated models using (**A**) method A at 2 years, (**B**) method A at 5 years, (**C**) method B at 2 years, (**D**) method B at 5 years, (**E**) method C at 2 years, (**F**) method C at 5 years, (**G**) method D at 2 years, and (**H**) method D at 5 years. The red dashed line represents the ideal calibration line where predicted risks perfectly match observed proportions. Blue points indicate the deciles of predicted risk, and the grey line represents a smoothed calibration curve

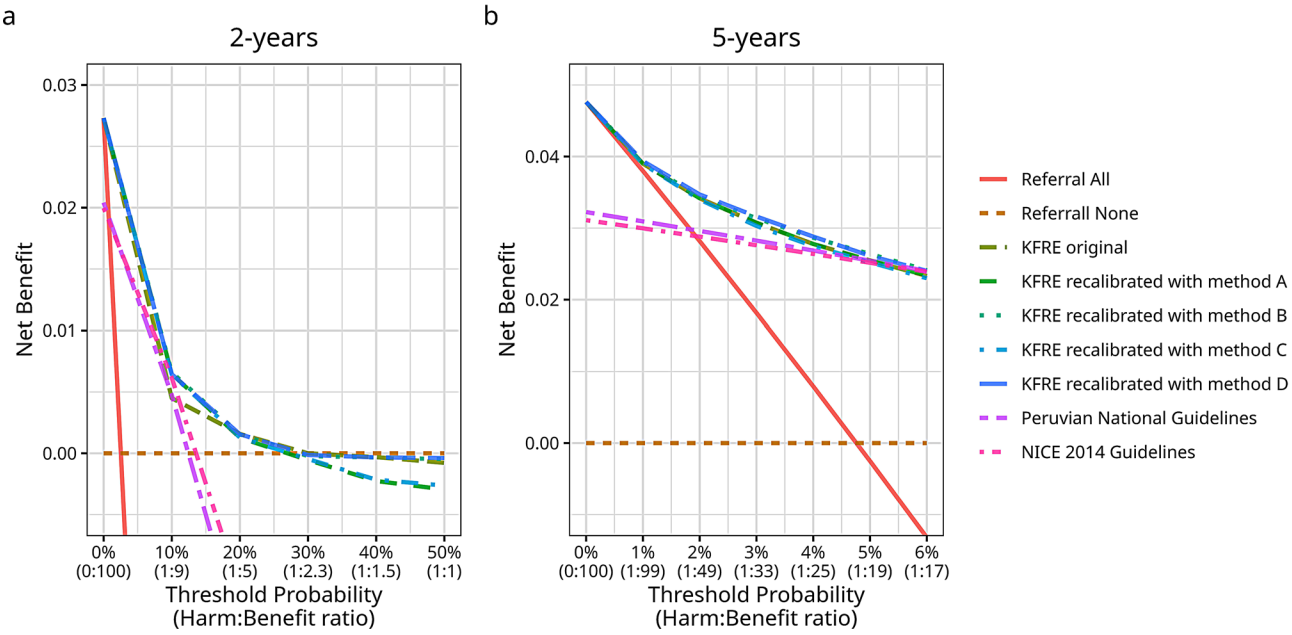

Fig. 6 Decision curve analysis (DCA) for the original and recalibrated KFRE models, and alternative nephrology referral guidelines (NICE 2014 and Peruvian National Guidelines). Net benefit is plotted against the threshold probability for the (**A**) 2-year and (**B**) 5-year horizon. The lines indicate the performance, in terms of net benefit, of different strategies: the original KFRE model, recalibrated KFRE models (Methods **A**, **B**, **C**, and **D**), Peruvian National Guidelines, NICE 2014 Guidelines, and the strategies of referring all or none. The net benefit values show how each strategy performs in balancing the correct identification of high-risk patients against minimising unnecessary referrals

death is 19.7% at five years, nearly four times the incidence of renal failure for the same period, making it likely that the Cox model would overestimate renal failure in these high-risk group. This explanation aligns with our observations and further supports our decision to exclude stage G5 patients, thereby validating the model in the specific outpatient context where it is intended to be applied.

A key finding of this study is that the KFRE model retains clinical utility despite its miscalibration. This can be understood through the net benefit framework, which emphasizes that a model may still be valuable if the miscalibrations occur infrequently or in less critical subpopulations. In this study, the overall miscalibration was most pronounced in patients at the extremes of risk, who represent a smaller fraction of the population. Most patients had reasonably calibrated risk predictions, contributing to a higher net benefit in clinical decision-making. Therefore, even with calibration issues, the KFRE model remains a robust tool for predicting kidney failure and guiding appropriate referrals, particularly in resource-limited settings where optimizing healthcare allocation is crucial. Importantly, this study is the first in Latin America to rigorously evaluate the clinical utility of the KFRE model, highlighting its potential role in enhancing CKD management strategies in the region.

Strengths and limitations of this study

A major strength of this study is its large sample size of 30,031 CKD patients, providing robust statistical power. Additionally, the use of VISARE surveillance data captures patients at primary healthcare centers nationwide, who are often identified through screening programs targeting individuals with diabetes, hypertension, or those over 55 years of age. This real-world data from a nationwide screening program at the primary care level reflects a population with characteristics that are both relevant and underrepresented in the literature, providing valuable insights into CKD management.

However, we excluded 22,627 patients due to missing eGFR and other critical variables, with most missing data attributed to albumin-to-creatinine ratio (ACR) measurements (60.7%). This raises concerns about the usability of KFRE in settings where ACR testing is limited, emphasizing the need to strengthen laboratory capacities, particularly outside of Lima, the capital of the country. In many regions, the lack of ACR data is primarily due to shortages of supplies, which limits the full implementation of risk prediction models like KFRE. To address missing data in our study, multiple imputation was performed under the assumption that data were missing at random (MAR). We included auxiliary variables such as age, sex, comorbidities, and lab values to make the MAR assumption more plausible and enhance the accuracy of the imputations. Nevertheless, the validity of this assumption cannot be guaranteed, which remains a limitation.

The geographical bias, with data predominantly from Lima, also underscores the need for further research in less-represented regions. Measurement errors in laboratory data, particularly outside of Lima, further highlight the necessity for improved healthcare infrastructure, including consistent access to ACR testing, to better support CKD risk prediction and management.

Implications for clinical practice and health systems

The KFRE model's superior net benefit for predicting kidney failure at 5 years offers a key opportunity for early referral for secondary prevention, allowing nephrology interventions to slow disease progression. For 2-year predictions, the model supports planning for renal replacement therapy or conservative treatment. Recalibrated KFRE versions outperformed current national referral strategies and NICE 2014 guidelines across various threshold probabilities. This aligns with NICE 2024's updated recommendation of a KFRE score > 5% or an ACR > 70 for nephrology referral.

In settings with limited nephrology resources, the KFRE's ability to identify high-risk patients can optimize referrals and prevent unnecessary ones. The use of a 3–5% risk threshold over 5 years has shown to be effective in various healthcare settings. Retrospective studies in Canada and the UK found that these thresholds reduced late referrals for patients progressing to kidney failure. Similarly, prospective evaluations noted shorter nephrology wait times, particularly for high-risk individuals.

However, the model's utility at 2 years requires caution. Net benefit analysis suggests an advantage at thresholds of 20–30%, but this diminishes at thresholds above 35–40%, where unnecessary referrals outweigh the benefits. For patients with higher risk probabilities, additional tests may be required to avoid premature dialysis preparations. Lower thresholds like > 20% can help optimize sensitivity, aiding in early dialysis planning or transplant referral.

Future research

Improving the KFRE model's calibration, especially for 2-year predictions, may require substantial updates, including re-estimating regression coefficients or modifying predictors. While promising, this approach risks overfitting and model instability. Therefore, using the current KFRE model remains more practical despite its limitations. Future studies should explore KFRE's predictive performance in subgroups like children, young adults, and those with diabetes, as emphasized by NICE 2024 guidelines. Assessing simplified versions of the model, such as the 3-variable KFRE or proxies like urine dipsticks, could also enhance its clinical applicability.

In addition, cost-effectiveness analyses should be conducted to evaluate the economic impact of implementing KFRE in clinical practice. Implementation studies examining the integration of KFRE into clinical workflows and trials that evaluate its impact on patient outcomes are needed to further establish its role in diverse healthcare settings.

Conclusion

Despite calibration issues, the KFRE model, especially in its recalibrated forms, remains a valuable tool for guiding nephrology referrals in Peru, providing a higher net benefit than current national guidelines. Its use can enhance early identification of high-risk patients, improving healthcare resource allocation in resource-limited settings. Further research is needed to refine the model, explore its utility in diverse subgroups, and integrate it effectively into clinical practice.

Abbreviations

ACR	Albumin-to-Creatinine Ratio
C-index	Concordance Index
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNSR	National Renal Health Center
DCA	Decision Curve Analysis
eGFR	Estimated Glomerular Filtration Rate
EsSalud	Social Health Insurance of Peru
ICD-10	International Classification of Diseases, 10th Revision
KFRE	Kidney Failure Risk Equation
KDIGO	Kidney Disease: Improving Global Outcomes
MAR	Missing At Random
NICE	National Institute for Health and Care Excellence
O/E ratio	Observed-to-Expected Ratio
RRT	Renal Replacement Therapy
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis
UMERC	Informatics application used to provide information to VISARE
VISARE	Renal Health Surveillance

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-025-04357-z.

Supplementary Material 1

Supplementary Material 2

Acknowledgements

Not applicable. No specific acknowledgements are necessary for this study.

Author contributions

JBZ served as the principal investigators, conceived the study concept, developed the proposal, contributed to the study design, coordinated the project, and participated in drafting the manuscript. PSB served as the co-principal investigator, conceived the study concept, developed the proposal, contributed to the study design, coordinated the project, was responsible for cleaning the raw data, conducting the analysis, and preparing the manuscript. EC co-authored the proposal, contributed to the study design, oversaw data acquisition, was responsible for cleaning the raw data, and assisted in drafting the manuscript. RCG, DZDO, and LCAG co-authored the proposal and contributed to the study design, oversaw data acquisition, and assisted in drafting the manuscript. co-authored the proposal, contributed to the study design and oversaw data acquisition. JBZ, PSB, EC and LCAG serve

as guarantors, ensuring the integrity of the study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding
This study was funded by the Instituto de Evaluación de Tecnologías en Salud e Investigación (IETSI) of EsSalud.

Data availability
The analysis code essential for the replication of study findings can be accessed at this link: https://github.com/psotob91/kfre-ckd-nationwide-essalud-peru. As per the privacy policies of EsSalud, the minimal data set is not open to public access. However, we are amenable to providing the anonymised data upon receipt of a reasonable request directed to the corresponding author (percys1991@gmail.com).

Declarations

Ethics approval and consent to participate
This study was approved by the Research Ethics Committee of the Edgardo Rebagliati National Hospital at EsSalud (Code No. 519-GRPR-ESSALUD-2023) and was conducted in accordance with the principles of the Declaration of Helsinki. A waiver of informed consent was granted by the Research Ethics Committee of the Edgardo Rebagliati National Hospital at EsSalud because the study involved routinely collected secondary data. Given the minimal risks associated with this type of research, this waiver was deemed a reasonable justification and was approved accordingly.

Consent for publication
Not apply.

Competing interests
JBZ, RCG, EPT, AVPV, and LCAG are full-time employees of EsSalud, serving as nephrologists at the Nephrology Department, Hospital Edgardo Rebagliati Martins, and the National Center of Renal Health in Lima, Peru. PSB was an associated researcher at the Instituto de Evaluación de Tecnologías en Salud e Investigación (IETSI), EsSalud, and has received consultancy fees from EsSalud. EJCP served as an associated researcher and Deputy Manager at IETSI, EsSalud. DDO was a full-time employee of EsSalud during the initial phases of the study. The authors affirm that their respective affiliations with EsSalud have not influenced any aspect of the study, including its design, data collection, analysis, interpretation, or manuscript preparation. Furthermore, none of the authors have any financial or personal relationships that could inappropriately influence (bias) the work reported in this manuscript. The authors declare that there are no other competing interests or potential conflicts of interest related to the content of this study.

Author details
[1]Nephrology Department, Hospital Edgardo Rebagliati Martins, EsSalud, Lima, Perú
[2]Centro de Innovación e Investigación Traslacional en Salud, Universidad Privada del Norte, Av. Tingo María 1122, Cercado de Lima, Peru
[3]Centro de Investigación en Salud Pública, Universidad San Martín de Porres and at Instituto de Evaluación de Tecnologías en Salud e Investigación – IETSI, EsSalud, Lima, Perú
[4]National Center of Renal Health, EsSalud, Lima, Perú
[5]Facultad de Salud Pública y Administración, Universidad Peruana Cayetano Heredia, Lima, Perú

Received: 25 November 2024 / Accepted: 21 July 2025
Published online: 05 December 2025

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