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Use of kidney failure risk equation to predict progression of end-stage renal failure in Turkish patients with stage 3–4 chronic kidney disease

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Abstract

Aim: The Kidney Failure Risk Equation (KFRE) is a useful tool for predicting chronic kidney disease (CKD) progression to end-stage renal disease (ESRD). It has been validated in various populations. This study aimed to evaluate the prognostic significance of the KFRE model in a Turkish CKD cohort.

Materials and Methods: In a prior retrospective study at a single center, the 4-variable KFRE model's accuracy in predicting ESRD progression was assessed. Among 246 stage 3 or 4 CKD individuals, two-year risk predictions categorized participants into low-intermediate (<20%) and high (≥20%) risk groups.

Results: The model showed a sensitivity of 48.9% (95% confidence interval [CI] 34.08–63.94) and a specificity of 89.45% (95% CI 84.32–93.35) in predicting kidney failure progression in the Turkish population with stage 3–4 CKD. The area under the receiver operating characteristic curve was 0.69 (95% CI 0.60–0.79, p = 0.0001). Albuminuria, glomerular filtration rate, and renin–aldosterone system blockage were independently associated with kidney failure progression according to the Cox regression analysis.

Conclusion: The findings of this study have demonstrated that the KFRE model shows potential utility in predicting the progression of stage 3–4 chronic kidney disease (CKD) toward the critical stage of ESRD for the Turkish population.

Introduction

Chronic kidney disease (CKD) is a medical issue characterized by persistent abnormalities in the structure or function of the kidneys, extending for duration of more than three months and having a negative effect on an individual's health. The categorization relies on the estimated glomerular filtration rate (eGFR) in addition to the existence of albuminuria [1]. Chronic diseases, such as cardiovascular diseases, diabetes mellitus (DM), and hypertension (HT), may contribute to CKD development [2].

Approximately 843 million people worldwide currently have CKD, and its prevalence is increasing. About 13.4% of people have CKD in stages 1–5, and 10.6% have it in stages 3–5. Around a third of individuals with CKD have accompanying conditions as DM and HT [3]. In Turkey, the CREDIT trial, a population-based study of CKD performed in 2011, revealed that the overall frequency of CKD was 15.7%. In stages 1, 2, 3, 4, and 5, 5.43%, 5.15%, 4.67%, 0.27%, and 0.15% of people had CKD, respectively [4].

Even though CKD classification is determined by serum creatinine levels along with eGFR, there is currently no established clinical decision-making model to predict CKD progression. Despite various markers, such as albuminuria, being tested in recent years to predict CKD progression, no appropriate method has been established [5]. In a multicenter study conducted by Tangri et al., various models were created for estimating the progression of CKD. Furthermore, the Kidney Failure Risk Equation (KFRE) was created, which includes crucial demographic information such as age and sex, along with laboratory data including eGFR and urinary albumin-creatinine ratio (UACR) [6].

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This model demonstrated good performance in its ability to make such predictions. This model has been tested in multiple countries, including England, Europe (e.g., Portugal), South Asia, and Singapore [6-9]. Therefore, the main goal of this study was to evaluate the applicability of the KFRE model in the Turkish population.

Materials and Methods

Study design

This retrospective study was conducted at a tertiary nephrology clinic center in Turkey. Participants with stage 3–4 CKD who were older than 18 years were included in the research. These individuals had been attending a nephrology outpatient clinic for at least two years between 2010 and 2016. Ethical approval was received from the Ethics Committee of Marmara University Faculty of Medicine (Ethics Committee Protocol code: 09.2016.499).

Study population and data source

The sample size for our study was determined by considering the proportion of patients who met the inclusion criteria and applied to our center, following accurate research methodology. This approach demonstrates the overall number of eligible patients that can be included in the study. Therefore, the sample size applied to our study was determined based on the number of eligible patients who were accessible during the study period.

Excluded from the study were patients with stage 1–2 and 5 CKD, acute glomerulonephritis, new-onset nephrotic syndrome, vasculitis, connective tissue disease, active infection, malignancy, decompensated heart failure, chronic liver disease, and renal transplant. The study included patients with data on sex, height, weight, age, smoking status, blood pressure, haemoglobin, parathormone, creatinine, UACR, blood urea nitrogen, sodium, potassium, albumin, calcium, phosphorus, and uric acid.

The eGFR was determined using the CKD-EPI formula: eGFR = 141 × min (Scr / k, 1) × max (Scr / k, 1) −1.209 eGFR 141 × min (Scr / × max (Scr / k, 1) × 0.993 year × 1.018 [female] × 1.159 [black race].

In this study, 2-year kidney failure development risk estimates were recorded using the 4-variable KFRE from the following website: https://www.qxmd.com/calculate/calculator_308/kidney-failure-risk-equation-4 variable.

End-stage renal disease (ESRD), or kidney failure, is clinically identified by a requirement of initiating chronic dialysis or undergoing kidney transplantation.

In Tangri et al.'s study, the patients were categorized into five distinct groups using the 2-year kidney failure risk equation. The groups were defined as 0% to 2%, 2% to 6%, 6% to 10%, 10% to 20%, and above 20% [6]. Based on the limited sample size, the participants were divided into two different categories depending on their risk level: the low-intermediate risk group with a risk percentage of less than 20%, and the high risk group with a risk percentage exceeding 20%.

Statistical analysis

The normal distribution for continuous variables was established through the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation or as median (interquartile range), depending on whether the Student t-test or the Mann–Whitney U test, respectively, was used. Testing for differences between categorical variables was done using the Chi-square test. The sensitivity and specificity were determined by analyzing the receiver operating characteristic (ROC) curve [10].

An analysis using Cox regression was performed to identify the independent risk factors linked to the progression of renal failure. Statistical analyses were performed using the IBM SPSS version 28.0 (IBM Corp., Armonk, NY, USA). P-values < 0.05 were considered statistically significant.

Results

A total of 340 patients were evaluated for eligibility, with 246 being enrolled in the present research (Figure 1). Among such individuals, 137 (55.7%) were male, with a mean age of 65.3 ± 12.4 years. The mean body mass index (BMI) in the study population was 29.4 ± 6.7 kg/m^2. The average systolic and diastolic blood pressure values at baseline were 149.2 ± 24.4 and 82.6 ± 14.8 mmHg, respectively. Table 1 displays the primary demographic and clinical characteristics of the study population.Baseline laboratory features of the patients are displayed in Table 2.

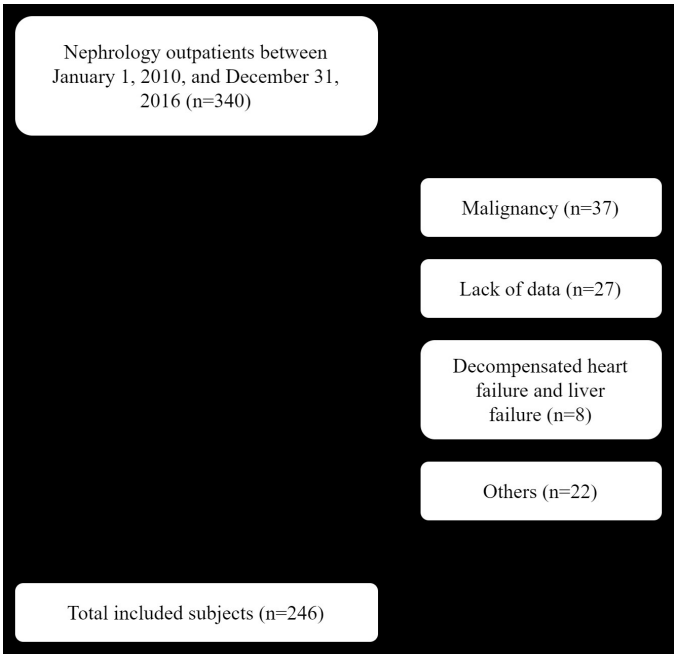

Figure 1. Diagram of the study population.

One hundred and twenty-five patients (50.8%) had stage 3 and one hundred and twenty-one patients (49.2%) had stage 4 CKD at the initial phase of the cohort trial. The median 2-year kidney failure development risk was calculated as 6.85% (0.12–57.5) using the 4-variable KFRE. According to our classification, 44 (17.9%) patients had high risk (risk >20%), and 202 (82.1%) had low–intermediate risk (risk <20%) for the development of kidney failure.

The mean eGFR was 26.3 ± 11.6 mL/min/1.73 m^2 at the end of 2 years. Moreover, 47 (19.1%) patients had kid-

Table 1. Baseline demographic and clinical data of the patients.

Parameter	Patients (n=246)
Gender	
Women, n (%)	109 (44.3)
Men, n (%)	137 (55.7)
Age (years)	65.3 ± 12.4 (23-89)
History of Smoking, n (%)	128 (52)
Systolic blood pressure (mmHg)	149.2 ± 24.4 (86-220)
Diastolic blood pressure (mmHg)	82.6 ± 14.8 (44-140)
Hypertension, n (%)	239 (97.2)
Diabetes mellitus, n (%)	139 (56.5)
ACE inhibitors or ARB usage, n (%)	151 (61.4)

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers. Values are given as mean ± SD (min-max) or number (percentage).

Table 2. Baseline laboratory data of the patients.

Parameter	
Hemoglobin (g/dL)	12.3 ± 1.6 (7.3-18)
BUN (mg/dL)	36.2 ± 13.5 (12-80.7)
Creatinine (mg/dL)	2.1 ± 0.6 (1.1-3.9)
Total protein (g/dL)	7.1 ± 0.6 (5.7-8.7)
Albumin (g/dL)	4.3 ± 0.4 (3-5.2)
Na (mEq/L)	140.2 ± 3.7 (122-154)
K (mEq/L)	4.9 ± 0.6 (3-6.5)
Ca (mg/dL)	9.4 ± 0.7 (6.5-14.6)
P (mg/dL)	3.8 ± 0.7 (2.2-5.4)
Parathormone (pg/mL)	116.5 (15-894)
Albuminuria (mg/day)	306.6 (5.1-6444.4)
eGFR (ml/min/1.73 m^2), estimated by CKD-EPI	31.8 ± 10.2 (15.2-59.4)

Values are given as mean ± SD (min-max)or median (inter-quartile range).

Table 3. The development of kidney failure according to baseline chronic kidney disease stages.

Baseline CKD Stage	The Development of Kidney Failure			p
	No, n (%)	Yes, n (%)	Total	
CKD Stage 3	116 (47)	9 (3.1)	125	
CKD Stage 4	83 (33.9)	38 (16)	121	<0.001
Total	199 (80.9)	47 (19.1)	246	

CKD, chronic kidney disease.

ney failure, of whom 38 (16%) had stage 4 CKD at the beginning (Table 3).

In addition, kidney failure developed in 24 (12%) of 202 patients with low–intermediate risk of kidney failure and 23 (52.2%) of 44 patients with high risk. In this retrospective study of 246 patients, the KFRE was found to have a sensitivity of 48.9% (34.08%–63.94%), specificity of 89.45% (84.32%–93.35%), positive predictive value of 52.3% (36.69%–67.54%), and negative predictive value of 88.12% (82.84–92.24). The area under the ROC curve (AUC) for the 4-variable KFRE model was 0.69 (95% CI 0.60–0.79) (p = 0.0001) (Figure 2).

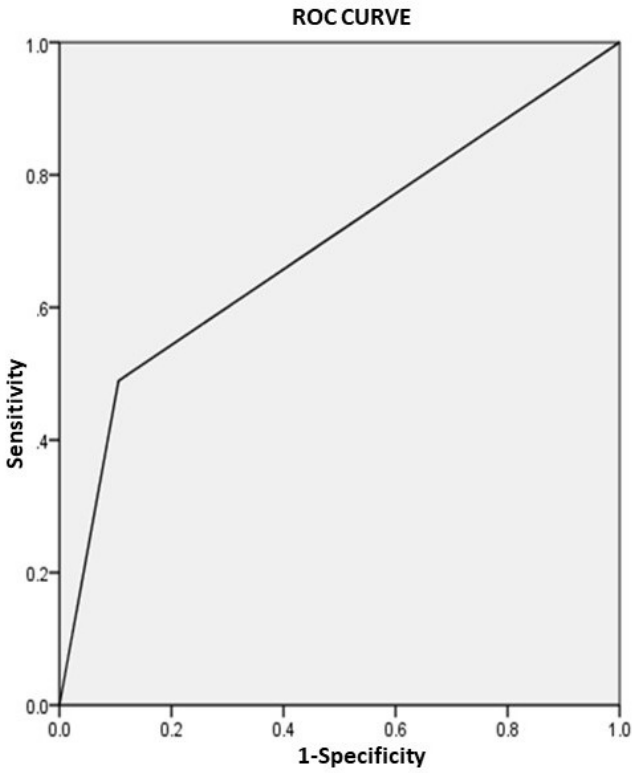

Figure 2. ROC-AUCs for 2-year kidney failure development risk estimates in patients with CKD stage 3 and 4 using "Kidney Failure Risk Equation".

In individuals who had stage 3 CKD, end-stage renal disease occurred in 9 (7.2%) out of 124 patients in the low–intermediate risk group, and in just one patient in the high-risk group. The KFRE was found to have a sensitivity of 0% (0%–3.6%), specificity of 90% (55.5–99.75), positive predictive value of 0% (0%–97.5%), and negative predictive value of 7.26% (3.37%–13.38%) in predicting ESRD development. KFRE did not reach statistical significance in the analysis of the high risk group because this group had only one patient.

Among patients with stage 4 CKD, ESRD developed in 15 (12.5%) of 78 patients in the low–intermediate risk group, and kidney failure developed in 23 (19%) of 43 participants in the high risk group. The KFRE was found to have a sensitivity of 60.53% (43.39%–75.96%), specificity of 75.90% (65.27%–84.62%), positive predictive value of 53.49% (37.65%–68.82%), and negative predictive value of 80.77% (70.27%–88.82%) in predicting kidney failure development. For patients with stage 4 CKD, the AUC for the 4-variable KFRE model was 0.68 (95% CI 0.58–0.79) (p = 0.001) (Figure 3).

In the univariate analysis, baseline serum albumin, calcium, phosphate, parathormone (PTH), albuminuria, eGFR, presence of diabetes, and angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) usage were significantly related to kidney failure development. Cox regression analysis revealed that only high urinary albumin (Exp B, 1.193; 95% CI 1.086–1.311; p = 0.0001), low GFR (Exp B, 0.911; 95% CI 0.876–0.948; p = 0.0001), and ACEi/ARB usage (Exp B, 1.876; 95%

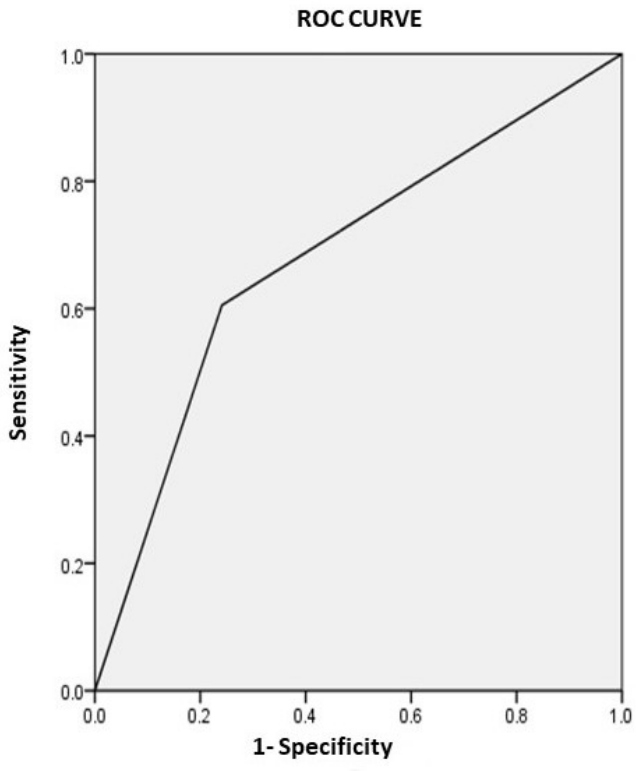

Figure 3. ROC-AUCs for 2-year kidney failure development risk estimates in patients with CKD 4 using "Kidney Failure Risk Equation".

CI 1.018–3.457; p = 0.04) were independent risk factors for kidney failure development.

Discussion

This study investigated the use of KFRE to predict the probability of kidney failure resulting in dialysis or transplantation within a two-year period for individuals with stage 3–5 CKD. We found that the 4-variable KFRE model effectively predicted which patients would develop ESRD within 2 years.

This risk prediction model relies on electronic medical records and laboratory data and aligns with the Kidney Disease Improving Global Outcomes (KDIGO) guideline [1]. The study by Tangri et al. included 3440 patients, with 27% having stage 3 CKD, 67.33% having stage 4 CKD, and 6% having stage 5 CKD [5]. When the model included four variables, it had a c-statistic of 0.91 [6, 11]. The addition of serum phosphorus, calcium, and bicarbonate levels in the model slightly increased the AUC [5, 12].

The utilization of KFRE, eGFR, and UACR in the evaluation allows the detection of individuals with a heightened likelihood of progressing to ESRD. This facilitates the timely referral of patients to nephrologists for the implementation of appropriate treatments [11]. The management of this condition may involve prompt initiation of renal replacement therapy or transplantation, along with a vascular intervention aimed at improving patient outcomes and potentially reducing the requirement for hospitalizations [12]. In addition, referral of high risk cases may contribute to a decrease in the overall prevalence of advanced CKD. As with other studies, our patient population was followed by nephrologists, and their outcomes may differ from those of similar patients followed by non-nephrologists [5, 13]. Furthermore, early referral of high risk cases to nephrologists may result in better patient outcomes [14].

In a meta-analysis, Tangri et al. evaluated the accuracy and precision of these equations in 31 cohorts over a period of approximately 4 years [6]. The analysis included approximately 700,000 patients with CKD, and kidney failure developed in 23,829 patients. The study included data from 16 cohorts from North America and 15 cohorts from Asia (Japan), Europe (Israel, Sweden, Netherlands, Germany, and UK), and Australia but did not include data from Turkey. With a mean age of 74 years and a baseline eGFR of 46 mL/min/1.73 m^2, the patients were classified as having 84% HT and 40% DM. The incidence of kidney failure ranged from 1.2 to 168.3/thousand/year. The probability of kidney failure predicted in the second year was >20% in 0.23%–50% of the cases. The 4-variable model had a c-statistic of 0.9 (95% CI 0.89–0.92) for the 2-year risk and 0.88 (95% CI 0.86–0.90) for the 5-year risk. In the meta-analysis, the 8-variable model had a c-statistic of 0.89 (95% CI 0.88–0.91) for the 2-year risk and 0.86 (95% CI 0.84–0.87) for the 5-year risk [6].

In the Mild to Moderate Kidney Disease study, the 4-variable model had a c-statistic of 0.79 (95% CI 0.72–0.87) for predicting the 2-year risk, whereas the Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the AIDS of Nurse Practitioners study found a c-statistic of 0.77 (95% CI 0.73–0.81) for predicting the 5-year risk [13, 15]. The RENAAL study, conducted outside of North America and including only patients with DM, had a c-statistic of 0.82 (95% CI 0.79–0.85) for predicting risk [16]. In the present study, which did not include patients with stage 5 CKD, the 4-variable model had a c-statistic of 0.69 (95% CI 0.60–0.79) for predicting the 2-year risk. Based on the outcomes of Ali et al., it was observed that individuals diagnosed with glomerulonephritis and diabetic nephropathy showed elevated risk scores. Conversely, the KFRE model exhibited limited efficacy in accurately predicting risk among patients with ADPKD [17]. The lower c-statistic value observed in the present study relative to other studies may be attributed to the absence of patients with glomerulonephritis in our patient population.

Understanding this risk equation is crucial in clinical practice to assess prognosis and guide treatment choices, including deciding when to establish vascular access for hemodialysis, inserting a peritoneal catheter for peritoneal dialysis, or pursuing preemptive transplantation. Further analysis is needed to determine optimal referral to nephrology centers when the 5-year risk is calculated as 3%–5% or planning of vascular access when the 2-year risk is calculated as more than 20%–40% [5, 6, 12].

There are a few limitations to this study. One potential limitation is the retrospective, single-center design, which could lead to bias in patient selection. Mortality was not included in the evaluation, which could have affected the results. Due to the limited population size, the accuracy of the KFRE was impacted. In addition, the follow-up

period was only 2 years; thus, 5-year results were not obtained. To the best of our knowledge, this is the first study in the Turkish population to evaluate the KFRE. The retrospective design of the study also prevented the use of the 8-variable model, including calcium, phosphorus, and bicarbonate, because of missing data.

Conclusion

Although the c-statistic value of KFRE for predicting kidney failure in the Turkish population with stage 3–4 CKD at the end of the second year is lower than that in the North American population, it is still comparable to the European cohort and statistically significant. To better determine the relevance of this equation in Turkish populations, further studies involving more patients from multiple centers are needed. Future analyses should also explore the influence of this risk equation in clinical practice.

Ethical approval

Ethical approval was received from the Ethics Committee of Marmara University Faculty of Medicine (Ethics Committee Protocol code: 09.2016.499).

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