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Research Article

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Can Kidney Failure Risk Equation (KFRE) Predict ESRD in The Norwegian Population? Validation of the KFRE Equation, 10 Years Data from Vestfold, Norway

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Abstract

Background: *Chronic kidney disease occurs in approximately 11% of the adult population, and about 0.3% develops end-stage renal disease (ESRD) requiring kidney replacement therapy. The Kidney Failure Risk Equation (KFRE) can predict 2 and 5-year risk of dialysis in patients with CKD stages 3 to 5. Having a tool to predict ESRD within 2-5 years is of value to prioritize health resources for patients with moderate to high risk. The method has been validated in several other countries.*

Objective: *To validate the KFRE method in a Norwegian population with CKD stages 3-5.*
Patients and Methods: A retrospective cohort study with 118 patients from Vestfold Hospital Trust, Norway.

Results: *The number of observed cases of ESRD requiring dialysis corresponded to increased KFRE-predicted risk. The KFRE predictions for 2 and 5-year risk of ESRD show an AUC of 0.66 (95% CI 0.53-0.77) and 0.62 (95% CI 0.52-0.74), respectively. This is consistent with findings from other countries. The results indicate that the KFRE method can also be very useful in clinical practice in Norway.*

Conclusion: *KFRE can predict ESRD requiring dialysis in the Norwegian population. It is desirable to validate the method in a larger Norwegian population for more reliable results.*

Keywords: Dialysis, Kidney Failure, Calculator, KFRE

1. Introduction

Chronic kidney disease (CKD) is a major global health problem with a prevalence of around 11%. World Health Organization (WHO) and Disability-Adjusted Life Years (DALYs) reports show that the proportion of people developing kidney failure is increasing, especially in countries with low gross domestic product (GDP) [1].

Complications and symptoms specific to CKD can be prevented, progression delayed, and often treated if patients are diagnosed and followed up adequately. Optimal follow-up and treatment can delay and, in the best case, prevent the disease from progressing to ESRD requiring dialysis or transplantation in many patients. According to The American Association of Kidney Patients, kidney care is characterized by late diagnosis, outdated dialysis technologies, reduced access to treatment, long waiting times for organ transplantation, and high mortality [2].

CKD increases the risk of cardiovascular events, death, and ESRD, which requires dialysis or kidney transplantation. In 2022, 2700 people received kidney replacement therapy in Norway, corresponding to approximately 988 people per million inhabitants, an increase of 1.8% since 2018 [3]. Patients with CKD also have a higher incidence of depression, physical inactivity, and skin itching, which are associated with reduced quality of life (QoL) [4]. CKD also poses a significant economic burden on society with increased healthcare costs [5].

Kidney function can be measured, but in daily practice, estimated glomerular filtration rate (eGFR) is used to estimate kidney function and define the degree of kidney failure. The method is inexpensive and readily available, unlike direct measurement of kidney function [6]. However, estimated GFR alone does not provide enough information about the risk for progression of kidney failure over time [7].

It is therefore important to find suitable and readily available parameters for the prognosis of CKD, especially the risk of developing ESRD requiring kidney replacement therapy. Can we use a method to identify patients at increased risk for kidney replacement therapy and perhaps prevent and prolong the time to ESRD? To investigate this, we wanted to validate the tool that Tangri et al. developed in 2011 in a Canadian population with CKD in a Norwegian population.

The tool is called the Kidney Failure Risk Equation (KFRE) and is used to predict the risk of ESRD in patients with CKD (8). KFRE is a tool for calculating the risk of progression to ESRD in patients with CKD stages 3 to 5. In the original development of KFRE, three variables were used (age, sex, eGFR). The model was then expanded to five variables and further developed into an eight-variable model that includes age, sex, estimated GFR, albuminuria, calcium, phosphate, bicarbonate, and albumin. The eight-variable model provides the most accurate prognosis. The KFRE model has till now been validated in Canada, Portugal, and the Netherlands [8-10].

2. Method

We conducted a single-center retrospective analysis of a cohort with CKD stage 5 in hemodialysis treatment in Vestfold Norway to validate KFRE. SPSS version 26 was used for statistical analyses [11, 12]. ROC curves (Area Under the Curve) were applied to assess how the KFRE method predicts ESRD [13, 14].

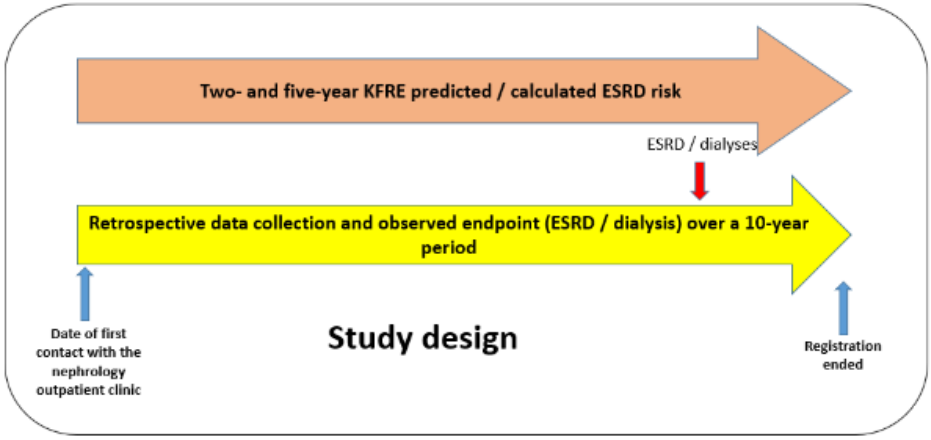

Figure 1: Study design

The cohort initially consisted of 226 individuals with CKD stage 5 in dialysis from the Vestfold Hospital Trust (VTH) in norway in the period 2009-2022. VHT is the central hospital in Vestfold County with approximately 256,000 inhabitants. We included all patients who had started dialysis (HD or PD) in the period 2009-2020 in VHT. The date of first contact at the nephrology outpatient clinic was the baseline for data collection, and the date of establishment in hemodialysis is the end date for data collection, with dialysis treatment as the endpoint.

Exclusion criteria were age under 18 years, patients with acute initiation of hemodialysis regardless of cause, and patients who died before dialysis treatment. Included variables were age, gender, systolic blood pressure, smoking, diabetes mellitus (type 1 and 2) and established cardiovascular disease.

Laboratory variables were eGFR, s-phosphate, s-albumin-corrected calcium, s-albumin, s-total CO2, and urine albumin/creatinine ratio. We applied the 8-variable model of KFRE to predict 2 and 5-year ESRD risk, which is divided into 3 risk categories: Low, medium, and high. Predicted risk was compared with the actual occurrence of the endpoint, which was dialysis treatment.

Figure 2: Flow Chart, Patient Inclusions

3. Results

We included 118 individuals, of whom 78 were men (66%) (Figure 2). The average age was 61 years (range 19-88 years). The causes of CKD were diagnosed to be hypertension (38%), T2DM (30%), glomerulonephritis (14%), others (unknown) (10%), and postrenal (9%). Eighty percent of patients were known to the outpatient clinic at least 2 years before CKD-5. A total of 29 patients (24%) developed dialysis-requiring kidney failure (CKD-5D) after 2 years, and 89 patients (64%) after 5 years. The average time to initiation of dialysis treatment was 4.7 years, with a median of 3.6 years (range 0.4-20 years). The death rate was 66 (60%) during the study period.

	Vestfold (n=118)
Age	61
Sex – men	78 (66%)
Diabetes	35 (30%)
Hypertension	45 (38%)
Glomerulonephritis	16 (14%)
Post-renal CKD	10 (9%)
Other / Unknown	12 (10%)
eGFR mL/min/1.73 m², mean	35
CKD stadium 3	46 (39%)
CKD stadium 4	49 (42%)
CKD stadium 5	9 (8%)
Calcium, mmol/L, mean	2.35
Phosphate, mmol/L, mean	1.26
Albumin, g/L, mean	38.0
Bicarbonate, mEq/L, mean	24.6
ACR below 30 mg/mmol	65 (55%)
ACR 30-300 mg/mmol	48 (38%)
ACR over 300 mg/mmol	12 (10%)

Table 1: Demographic data for the Vestfold cohort (n=118).

The two-year and five-year risk of dialysis was calculated in KFRE eight variable calculator for all 118 individuals in the cohort. The results were significantly different for the low, medium, and high-risk categories ($p < 0.004$) (Figure 3). The observed two-year and five-year incidence of dialysis corresponded well with the KFRE-predicted risk of dialysis.

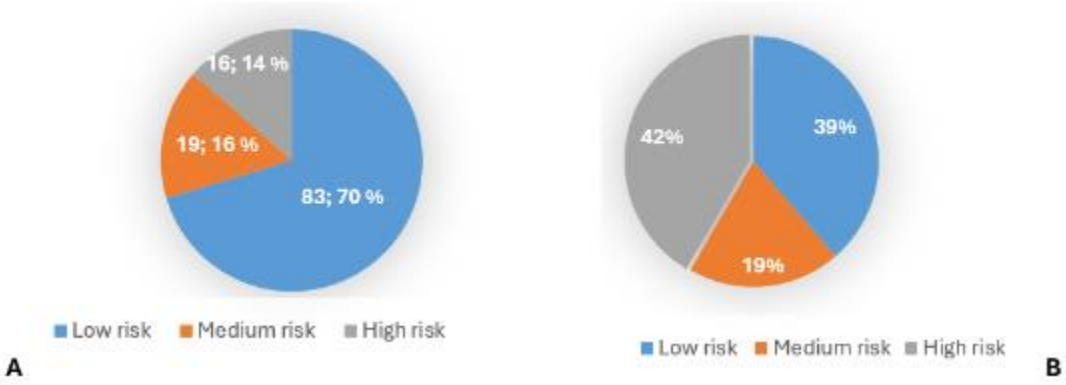

Figure 3: Two-year (A) and five-year (B) predicted dialysis risk.

KFRE-predicted two and five-year risk of dialysis for all 118 individuals at baseline was compared with the two and five-year observed incidence of dialysis.

The two-year risk of dialysis was calculated to be 28.8% (70% in low risk, 16% in medium risk, and 13% in high-risk category). The difference between two-year risk categories for dialysis was

significant (p<0.004).

The five-year risk of dialysis was calculated to be 68% (39% in low, 19% in medium, and 42% in high-risk category). The difference between categories was significant (p<0.004).

Figures 4 and 5 compare the two-year and five-year predicted risk of dialysis with the observed dialysis rates, respectively.

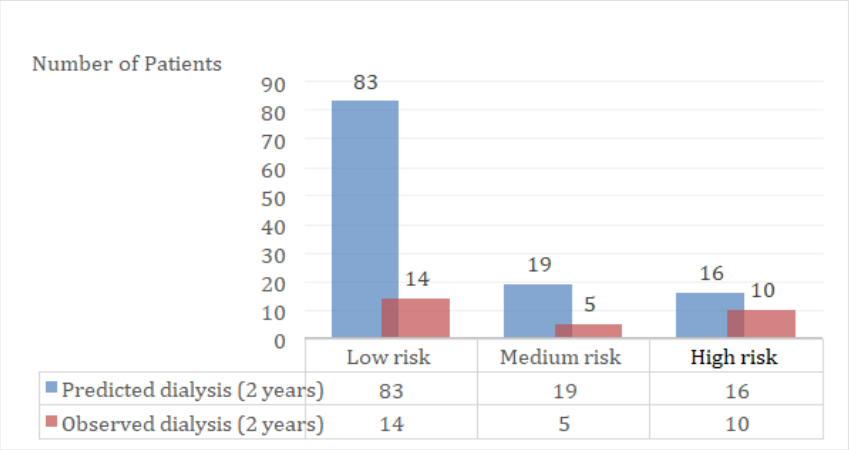

Figure 4: Two-year risk of dialysis compared with Two-year observed dialysis incidence.

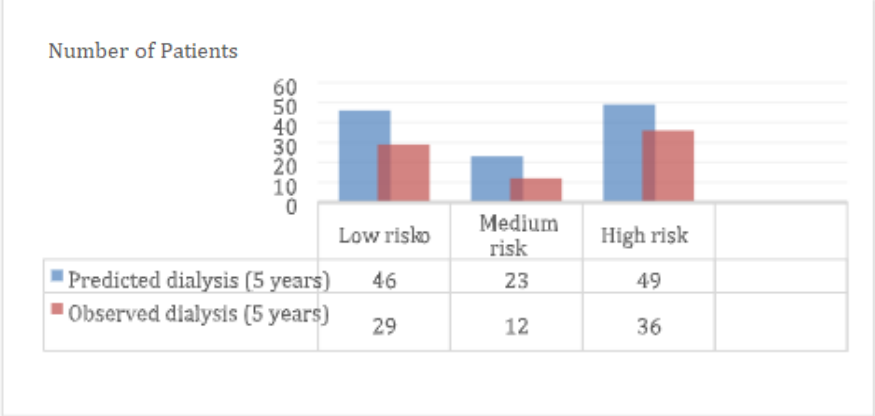

Figure 5: Five-year risk of dialysis compared with 5-year observed dialysis incidence.

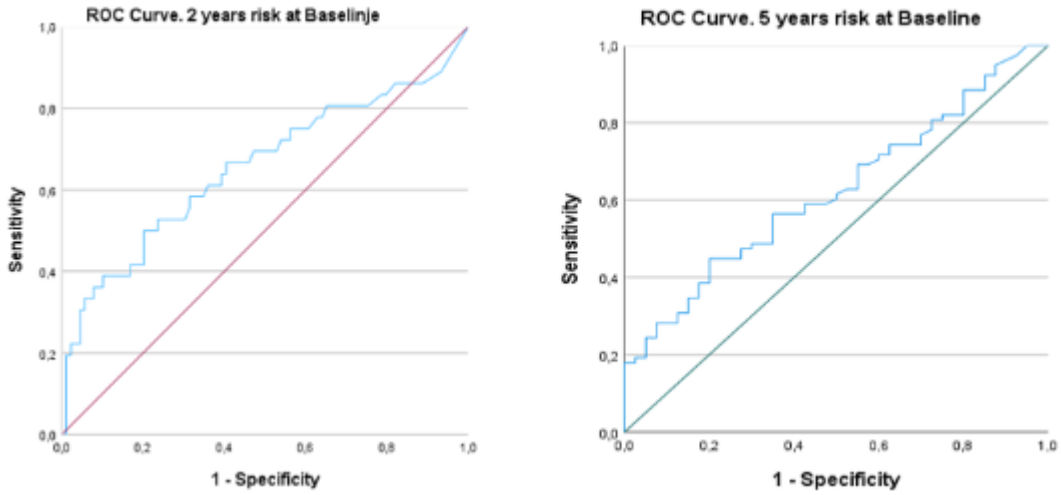

Figure 6: ROC curves. Two- and five-year ESRD prediction with KFRE calculator

The AUC value was 0.66 (95% CI 0.53-0.79) for 2-year risk of dialysis and 0.62 (95% CI 0.52-0.72) for 5-year risk of dialysis.

4. Discussion

The cohort consisted of 118 patients who received dialysis treatment at our center over 10 years. Although the population was relatively small compared to other studies, the cohorts characteristics regarding age, cause of ESRD, and comorbidity are representative of the Norwegian population with ESRD from the Norwegian Renal Registry (NNR 2022). As in NNR 2022 data, the most common causes of ESRD were hypertension 44%, diabetes 18%, and glomerulonephritis 14%. For comparison, the respective figures from NNR were 38%, 18%, and 14%. Diabetes was a somewhat more frequent cause of ESRD in this study cohort. Our patients have the same age as the Dutch cohort, while the cohorts from Portugal and Canada were significantly older. It is important to emphasize this difference, as age is one of the strongest independent risk factors for ESRD [8, 10]. Large age variation can both over- and underestimate the risk of dialysis due to multifactorial reasons.

We used ROC curves to assess how well KFRE predicts the risk of dialysis in the cohort. The AUC value was 0.66 for 2-year risk of dialysis and 0.62 for 5-year risk of dialysis. ROC curves and AUC values are important tools for assessing the performance of predictive models. An AUC value of 0.5 represents a random guess, while a value of 1.0 represents a perfect prediction [14]. The AUC values of 0.62 and 0.66 in this cohort indicate that the models have a moderate ability to distinguish between patients who will need dialysis within 2 and 5 years, respectively, and those who will not.

KFRE emphasizes proteinuria as a strong prognostic risk factor for dialysis. This is a well-known, independent risk factor with high predictive value. Proteinuria is extensively discussed and specified as a significant modifiable risk factor for ESRD in the KDIGO guidelines [15].

The prevalence of severe proteinuria with Urine-ACR above 300 mg/mmol was 10% in our cohort, which is markedly lower compared to the prevalence in the Dutch study (42%) and the Canadian cohort (43%). This difference is significant and can likely explain most of the difference in dialysis risk in our cohort compared to findings from the Netherlands and Canada. Our cohort has more similarities with the Dutch cohort in terms of age, gender, and average eGFR. The cohort from Canada was significantly older but with comparable eGFR.

The proportion of individuals with predicted and observed 5-year medium risk for dialysis was lower than in the low-risk category. This may be due to small numbers with random variation. Predicted risk of dialysis distributed in different risk categories correlates well with observed incidence of dialysis.

Our findings have some limitations. The size of 118 patients creates uncertainty in the estimates. At the same time, we see many similarities in patient characteristics compared to data from NNR. Comparison with patient characteristics from other countries (Netherlands, Portugal, Canada) shows good agreement, especially with the Dutch population.

Laboratories in Norway have not yet implemented the KFRE calculator, and there is no current information on whether the nephrology community in Norway is considering to introduce KFRE in current practice. It is also not known whether the community will recommend the use of KFRE in primary healthcare for assessing individual patients' risk of dialysis as a basis for referral to specialist healthcare.

The method is validated and widely discussed in the literature. Our findings show that there is good potential for the use of KFRE to improve stratification of patients with low, medium, and high risk for development of ESRD. Risk prediction can be used to prioritize referral and follow-up of patients in specialist healthcare, as well as for treatment and follow-up of CKD patients in primary healthcare.

In 2022, a systematic review of studies focusing on the effect of KFRE in clinical practice showed that KFRE is extensively validated and used in referral to nephrologists, who can then inform the patient about the need for dialysis and plan this in good time. However, studies looking at clinical and economic outcome measures in practice are lacking [16]. Furthermore, ongoing randomized studies aim to increase the quality of evidence-based care for CKD patients [17, 18]. There is a need for more awareness and focus on CKD care, as late diagnosis and late referral to specialists are correlated with poorer quality of life, increased resource use, and reduced survival [19].

Although KFRE has not been implemented in Norwegian laboratories, there are web-based calculators where all variables can be entered manually, and the risk is calculated automatically. The model only predicts 2 and 5-year risk of dialysis and is not valid to predict the risk of ESRD development beyond this time. One contributing factor to this is the modern modification of clinical risk factors in CKD stage 3, which will delay the risk by several years more than the original calculator shows [20].

KFRE is not validated for kidney transplant recipients in terms of graft survival prognosis [21]. There are several factors in kidney transplant recipients that complicate risk assessment, so studies remain to be done to show whether KFRE is also relevant for use in this patient group.

It is important to emphasize that the KFRE method is only for use in patients with CKD with a complete investigation of the causal factors, and it can not be used for risk prediction in patients with acute kidney failure and unclear causal mechanisms. As mentioned, about 11% of the population in Norway has CKD. Most have mild to moderate CKD and a low risk to end up in ESRD requiring dialysis or transplantation. One can speculate that without access to risk prediction, many patients must be followed to avoid one

patient ending up with dialysis needs. This can be insurmountable even in Norway, unless some form of patient prioritization is done to get the best and appropriate use of available resources. The KFRE method may be suitable for this purpose.

5. Conclusion

Our findings show that the KFRE method has the potential to predict the risk of ESRD in patients with CKD in Norway. Although our cohort was relatively small, patient characteristics correspond well with national and international data. Further research and validation in larger populations are necessary to confirm these results and assess the method's clinical and economic effect.

Ethics: The study was approved by the Norwegian Center for Research Data (NSD) with study number 597782. Data was collected from a local quality register anchored in the clinic management. Personal information and register data were anonymized.

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