

## Kidney Failure Risk Equation predictive tool to improve predialysis patient management?

### Articoli originali

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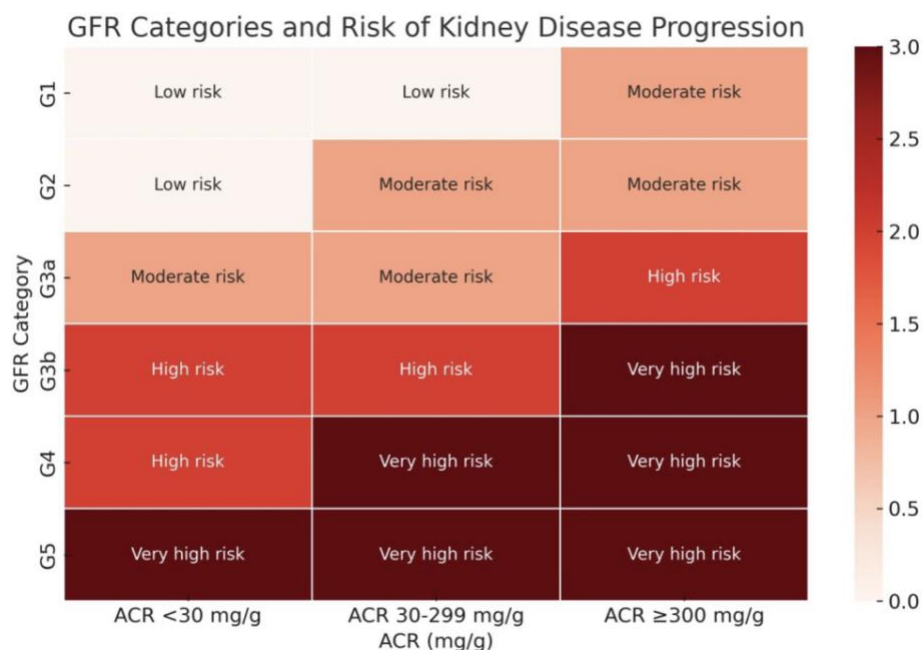
#### ABSTRACT

The Kidney Failure Risk Equation (KFRE) is a predictive tool that estimates the risk of progression to end-stage renal disease (ESKD) in patients with chronic kidney disease (CKD). This study evaluated the systematic implementation of KFRE in our nephrology center to improve the management of pre-dialysis patients. Through the analysis of 100 patients followed in the pre-dialysis pathway in the last 36 months, we observed a significant reduction in the initiation of dialysis in late referral mode, a lower use of temporary central venous catheters and an increase in timely preparation of vascular or peritoneal access. The comparison with historical pre-implementation data (2017-2020) highlighted an improvement in clinical organization and patient awareness in the choice of dialysis modality. The KFRE has proven to be a valid tool for risk stratification, optimizing the timing of renal replacement therapy and improving the allocation of healthcare resources. The integration of KFRE into clinical practice could represent a step towards precision nephrology, promoting more informed and personalized therapeutic decisions.

**KEYWORDS:** KFRE, CKD, vascular access, peritoneal access

## Introduction

Kidney Failure Risk Equation (KFRE) is a predictive tool that estimates the risk of progression to end-stage kidney disease (ESKD) in patients with chronic kidney disease (CKD). It represents a system validated by nephrology specialists to provide better personalized management of patients and evaluate the appropriate moment to plan the timing of starting renal function replacement treatment by planning all preparatory interventions (setting up vascular access/peritoneal catheter or pre-emptive kidney transplant). KFRE calculates risk over a 2- or 5-year period using 4 key variables, commonly available in medical records: age (in years), sex (male or female), eGFR (estimated glomerular filtration rate, expressed in mL/min/1.73 m<sup>2</sup>), UACR (urine albumin/creatinine ratio, expressed in mg/g). The calculation of the KFRE is based on a mathematical equation that uses the values of the variables indicated above. Equation details include specific coefficients for each variable (e.g., age, gender, eGFR, and UACR). The result is expressed as a percentage chance of developing kidney failure within 2 to 5 years. To facilitate the calculation, there are online calculators and tools integrated into clinical software on platforms that only require the entry of the 4 variables to quickly provide the result. UKidney's KFRE calculator offers a useful interface to enter the required data and obtain a risk estimate [1]. Results can be interpreted as low risk (<5%) with minimal likelihood of progression to renal failure; intermediate risk (5%-20%) patients who may require intensive monitoring and management; high risk (>20%) active planning for dialysis or transplant, with priority in clinical management. The calculator also includes a table that classifies patients by eGFR categories (G1: eGFR  $\geq$ 90 (Normal or High), G2: eGFR 60-89 (Slightly Reduced), G3a: eGFR 45-59 (Slightly-Moderately Reduced), G3b: eGFR 30-44 (Moderately-Severely Reduced), G4: eGFR 15-29 (Severely reduced), G5: eGFR <15 (Renal insufficiency) ) and albuminuria levels (A1: <30 mg/g (Normal or slightly increased), A2: 30-299 mg/g (Moderately increased), A3:  $\geq$ 300 mg/g (Severely increased) (Figure 1). A possible alternative to the traditional UKidney calculator is the calculator <https://kidneyfailurerisk.com> which can offer more advanced options with an eight variable version (calcium, phosphorus, bicarbonates, albumin) with better risk stratification and more accurate planning. Certainly UKidney is an easy calculator to use in daily outpatient practice.



**Figure 1. GFR categories and risk of kidney disease progression.**

The KFRE uses few but relevant clinical parameters, making risk calculation quick and easy. It allows you to estimate the progression of CKD so you can initiate preventative treatments and plan renal replacement options before the onset of ESKD. This can motivate the patient to follow medical recommendations, adopt a healthy lifestyle and reduce risk factors. Despite the reliability of the KFRE, it has some limitations. The cohorts used for its validation may not represent all populations, limiting accuracy in some ethnic groups or in patients with significant comorbidities. The availability and quality of data influence the accuracy of the score. For example, ACR is not always measured in patients with CKD; exclusion of some risk factors: variables such as the presence of diabetes or hypertension are not directly included in the model, even if they influence the risk of CKD progression [2].

The study by Ingwiller et al. validated the effectiveness of the 40% threshold of 2-year risk calculated with the renal failure risk equation (KFRE) for planning vascular access in patients with chronic kidney disease (CKD). The research, conducted on a retrospective French cohort, compared the KFRE model with the traditional criterion of estimated glomerular filtration rate ( $eGFR < 15 \text{ mL/min/1.73 m}^2$ ), demonstrating a better predictive capacity of the 8-variable model compared to the 4-variable one. The results indicate that the use of the 40% threshold of the KFRE guarantees personalized support in the management of patients with CKD by optimizing the time for the packaging of arteriovenous fistulas and the risk of starting dialysis with a central venous catheter [3].

A study conducted by Grams et al. evaluated the potential application of the KFRE using CKD-EPI 2021 for eGFR estimation, incorporating cardiovascular comorbidities as a variable. The analysis, based on data from 59 cohorts and 312,000 patients, compared this approach with the standard model and highlighted that KFRE shows high specificity in patients with  $eGFR < 45 \text{ ml/min/1.73 m}^2$  and in elderly. The model showed significant results in elderly patients with  $eGFR 45\text{--}59 \text{ ml/min/1.73m}^2$  especially in a long-term horizon. However, the integration of new variables did not bring significant improvements in the prediction of development of end-stage renal disease [4]. An external validation study conducted by Gallego-Valcarce et al. examined the effectiveness of KFRE and Grams predictive models in determining the risk of kidney failure and mortality in a cohort of Spanish patients with advanced (stage 4) chronic kidney disease (CKD). The analysis involved 339 patients followed for up to 5 years. Both models demonstrated excellent discrimination for renal failure, with AUCs ranging from 0.823 to 0.897. Furthermore, the Grams model provided reliable estimates of mortality before renal failure, with AUCs of 0.708 and 0.744 for the 2- and 4-year periods, respectively. Although both models showed adequate calibration for renal failure, the Grams model tended to overestimate mortality risk.

These results confirm the usefulness of predictive models in supporting personalized clinical decisions for patients with advanced CKD in Southern Europe [5]. The study conducted by Whitlock et al. validated the KFRE in a Manitoba population highlighting a high predictive capacity in the development of kidney failure in the following five years. A cohort of 1512 patients CKD stages three, four and five was examined. The analysis showed that KFRE is more specific than eGFR in discriminating high-risk patients with an area under the curve (AUC) of 0.90 compared to 0.78 for eGFR. Using a 5-year risk threshold of 3%, the KFRE achieved a sensitivity of 97% and a specificity of 62% for identifying high-risk patients. This study reiterates the importance of integrating KFRE in the management of patients with chronic renal failure by providing support to the nephrologist's clinical decisions and optimizing resources [6]. The study conducted by Chu et al. evaluated the usefulness of KFRE together with eGFR in predicting the time to develop the stage of end-stage chronic renal failure in patients with advanced CKD. 1641 patients in outpatient follow-up in the United States were considered and the results showed that KFRE has a high specificity (C-statistic: 0.862; 95% CI: 0.838–0.889) in estimating the timing of dialysis initiation or kidney transplant eligibility. The results

showed that KFRE was more accurate than eGFR in temporally estimating renal failure progression in patients with  $eGFR \geq 20$  mL/min/1.73m<sup>2</sup>, while it showed no benefit in patients with advanced CKD  $eGFR \leq 15$  mL/min/1.73m<sup>2</sup> or KFRE risk >40%.

These findings suggest that KFRE can improve clinical decision planning, such as vascular access preparation, and provide patients with more intuitive and precise prognostic information [7]. The use of the KFRE as a tool to improve vascular access (VA) planning in patients with advanced chronic kidney disease has received increasing attention. Marques da Silva et al. have highlighted how the addition of a KFRE threshold  $\geq 40\%$  to the traditional criterion of  $eGFR < 20$  mL/min/1.73m<sup>2</sup> can significantly improve the adequacy in the creation of arteriovenous fistulas or grafts (AVF/G). In their studies, the adoption of this combination allowed to increase the proportion of patients starting dialysis with AVF/G, while reducing unnecessary interventions. Furthermore, a retrospective study highlighted that a KFRE cut-off  $\geq 20\%$  has high sensitivity and specificity (72.8% and 78.4% respectively) for predicting the need for dialysis within two years. These results highlight the potential of the KFRE as a complementary tool to optimize the management of patients with CKD, suggesting the need for further validation in different population cohorts [8]. The study evaluated the use of KFRE in vascular access planning in patients with CKD. 256 patients with advanced CKD who underwent arteriovenous fistula or preemptive transplantation between 2018 and 2019 were retrospectively analyzed. The use of the KFRE proved accurate in predicting the need for the start of renal replacement therapy within two years. Patients with KFRE > 20% showed a significantly increased risk of initiating dialysis (HR 9.2; 95% CI: 5.06–16.60;  $p < 0.001$ ) and a shorter mean time between vascular access creation and initiation of dialysis ( $10.8 \pm 9.4$  months vs  $15.6 \pm 10.3$  months;  $p < 0.001$ ). Even in patients with  $eGFR < 20$  mL/min/1.73m<sup>2</sup>, KFRE >20% remained a significant predictor of dialysis initiation within 2 years (HR 6.61; 95% CI: 3.49–12.52;  $p < 0.001$ ). These results suggest that KFRE can be used to identify patients with higher priority for vascular access creation in patients with  $eGFR < 20$  mL/min/1.73m<sup>2</sup> combined with KFRE >20% [9]. KFRE represents a fundamental predictive tool for risk stratification in patients with chronic kidney disease.

A study conducted at Johns Hopkins Medicine demonstrated that the integration of the KFRE into computerized medical records increases the sensitivity of the nephrologist regarding the specific risk of progression of kidney disease. However, to date its use remains limited and variable and influenced by factors such as access to laboratory data, understanding of risk thresholds and the sensitivity of medical and nursing staff. It has been observed that the use of KFRE is fundamental for crucial decisions for the evolution of chronic kidney disease, promoting awareness of both healthcare personnel and patients for the choice of timing for planning the dialysis modality and with all the consequent actions such as the preparation of the vascular access or the positioning of the peritoneal catheter or the possible candidacy for pre-emptive kidney transplantation. Experience suggests that targeted training of healthcare personnel together with standardization of guidelines could amplify the use of KFRE by improving the clinical management of high-risk patients [10]. The use of the KFRE could also be extended to general practitioners through integration into electronic medical records, increasing awareness of each patient's risk. This would help improve the appropriateness of referrals to nephrologists and support shared decision-making regarding the initiation of dialysis, ultimately contributing to optimized management of CKD.

International validation of this tool has shown that the four-variable KFRE (age, sex, eGFR, urinary albumin-creatinine ratio) is particularly effective in short-term prediction of progression to end-stage renal disease. However, KFRE adoption varies significantly across national contexts, highlighting the need for specific adaptations to reflect local peculiarities, including demographic patterns and clinical practices. In Italy, the integration of KFRE could improve the efficiency of the healthcare system, reducing unnecessary referrals and concentrating resources on high-risk

patients, in line with the principles of personalized and sustainable medicine [11]. Management of CKD requires accurate prediction of the risk of progression to ESKD to optimize educational strategies and clinical interventions. Recent studies have shown that the KFRE represents a valid and calibrated tool for estimating the 2- and 5-year risk of ESKD, exceeding intuitive estimates by nephrologists in terms of accuracy and precision. Unfortunately, the adoption of KFRE in daily clinical practice is still limited, resulting in many patients starting dialysis in late referral. Greater sensitivity of the KFRE model in medical practice suggests a potential use to identify high-risk patients with the initiation of timely treatment and with adequate programming of the dialysis modality most suitable for the patient (hemodialysis with creation of arteriovenous fistula for dialysis or peritoneal catheter) and a possible reduction in the use of temporary central venous catheters in the initiation of renal replacement therapy. These results highlight the importance of integrating standardized predictive tools such as the KFRE into healthcare policies to improve the management of patients with CKD [12].

## Materials and Methods

Over the past 36 months, our nephrology center has implemented the systematic use of the KFRE in predialysis clinics to improve the management of patients with advanced CKD. The study involved a total of 100 patients followed in the predialysis process, in which the application of the KFRE guided clinical decisions relating to the timing of starting renal replacement therapy. KFRE was calculated using eight variables: age (years), sex (male/female), eGFR (estimated glomerular filtration rate according to CKD-EPI), UACR (urinary albumin-creatinine ratio in mg/dl), serum calcium level (mg/dl), serum bicarbonate (mEq/L), serum albumin (g/dl). The values obtained made it possible to stratify the individual risk of progression towards end-stage renal disease (ESKD) and to plan all preparatory interventions for the start of dialysis. The calculation of the KFRE was carried out using the equation available on the official Kidney Failure Risk Equation website [1]. The main indicators analyzed in the study were: the reduction in the proportion of patients who started dialysis in late referral mode (i.e. with insufficient or no preparation before starting renal replacement treatment), the decrease in the use of temporary central venous catheters as the first access for hemodialysis, the increase in patient awareness in the choice of dialysis method (peritoneal dialysis or hemodialysis), thanks to a more structured education path, the increase in the percentage of patients with a native vascular access or with a peritoneal catheter packaged in adequate times before the start of dialysis.

## Results

The collected data were analyzed retrospectively, comparing the results obtained with the historical pre-implementation data of the KFRE. In the three-year period 2017-2020, out of a total of 92 patients followed in predialysis clinics, 25% (23 patients) started dialysis with a temporary central venous catheter, 21.7% (20 patients) with a peritoneal catheter before starting dialysis, 38% (35 patients) with an arteriovenous fistula and 15.2% (14 patients) with a tunneled central venous catheter. In the three-year period 2021-2024, following the implementation of the KFRE, out of a total of 100 patients, only 5% (5 patients) started dialysis with a temporary central venous catheter, 35% (35 patients) with a peritoneal catheter before starting dialysis, 50% (50 patients) with an arteriovenous fistula and 10% (10 patients) with a tunneled central venous catheter (tCVC).

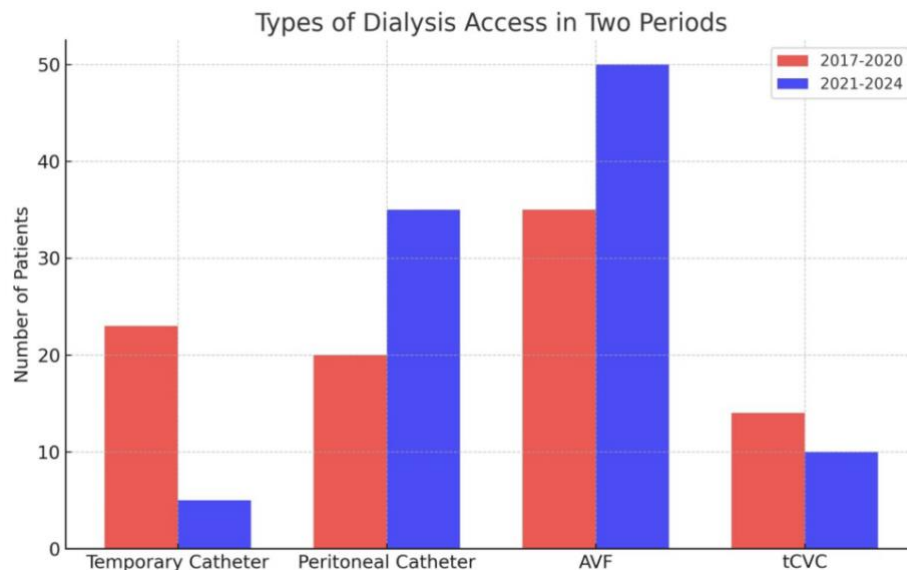


Figure 2. Types of dialysis access in two periods.

## Discussion

The KFRE not only helps nephrologists predict the progression of chronic kidney disease, but also provides important decision support for planning arteriovenous fistula (AVF) packaging. The indication and timing for starting an AVF are crucial in the management of patients approaching dialysis, and the KFRE allows for more informed decisions in this regard [13]. Using parameters such as eGFR and albuminuria, the KFRE provides a clear estimate of the 2- or 5-year risk of end-stage renal disease (ESRD). In patients with high short-term risk (for example, greater than 20% at two years), it is recommended to consider AVF packaging early to be ready for the possible start of dialysis. Intermediate-risk patients can benefit from gradual and monitored preparation, allowing nephrologists to schedule AVF packaging only when necessary, avoiding premature invasive procedures [14]. Timely packaging of the AVF, guided by the KFRE, reduces the risk of complications and the possibility of depending on temporary catheters, which increase the risk of infections and other associated complications [15]. The KFRE allows nephrologists to intervene at the right time, when the risk of progression is high but not yet critical. In patients with a very low risk of rapidly progressing to dialysis, KFRE allows us to avoid early packaging of the AVF, which may be unnecessary. This saves costs and avoids unnecessary interventions for the patient. Together with other clinical parameters (such as the rate of decline of GFR and the patient's age), the KFRE provides a basis for more precisely establishing the timing of the AVF, particularly useful for elderly patients or those with comorbidities, for whom an invasive intervention could pose greater risks [16]. Nephrologists can make more informed, risk-based decisions regarding AVF packaging. This helps reduce complications, optimize resources and improve the quality of care, ensuring that each patient receives the intervention at the right time. From here it follows that it is possible to stratify patients at different risk: high risk (e.g. >20% at 2 years): consider packaging the AVF quickly, with close monitoring; moderate risk (e.g. 10-20% at 2 years): frequent monitoring, with evaluation for packaging AVF if risk increases; low risk (<10% at 2 years): no immediate need to prepare the AVF; the patient can be followed up with regular follow-ups [17].

If the KFRE demonstrates a good level of accuracy, it could represent a useful tool to support the nephrologist in decisions regarding the management of patients with CKD. The integration of KFRE into clinical practice could facilitate risk stratification, optimize the timing of replacement therapies

and improve the management of healthcare resources. The KFRE could also help reduce the anxiety of CKD patients by providing a more realistic prediction of the risk of disease progression. The validation of the KFRE is the first step towards personalized medicine in the management of CKD with better quality of care and efficient management of resources. The integration of KFRE in the daily work of nephrology specialists will be able to promote the development of precision nephrology at the service of patient health and the sustainability of the system. Furthermore, the validation of the KFRE could increase patients' motivation to follow medical recommendations by adopting a healthy lifestyle aimed at reducing risk factors.

## **Conclusion**

In this study was documented that the implementation data of the KFRE notoriously reduced the percentage of patients who had started dialysis with a temporary central venous catheter, in comparison to the before KFRE implementation period.

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