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ORIGINAL ARTICLE

Kidney Failure Risk Equation in vascular access planning: a population-based study supporting value in decision making

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ABSTRACT

Background. The Kidney Failure Risk Equation (KFRE) can play a better role in vascular access (VA) planning in patients with chronic kidney disease (CKD) requiring hemodialysis (HD). We described the VA creation and utilization pattern under existing estimated glomerular filtration rate (eGFR)-based referral, and investigated the utility of KFRE score as an adjunct variable in VA planning.

Methods. Patients with CKD aged ≥18 years with eGFR <20 mL/min/1.73 m^2 who chose HD as dialysis modality from January 2010 to August 2020 were included from a population-based database in British Columbia, Canada. Modality selection date was the index date. Exposures were categorized as (i) current eGFR-based referral, (ii) eGFR-based referral plus KRFE 2-year risk score on index date (KFRE-2) >40% and (iii) eGFR-based referral plus KFRE-2 ≤40%. We estimated the proportion of patients who started HD on arteriovenous fistula/graft (AVF/G) within 2 years, indicating timely pre-emptive creation, and the proportion of patients in whom AVF/G was created but did not start HD within 2 years, indicating too-early creation.

Results. Study included 2581 patients, median age 71 years, 60% male. Overall, 1562(61%) started HD and 276 (11%) experienced death before HD initiation within 2 years. Compared with current referral, the proportion of patients who started HD on AVF/G was significantly higher when KFRE-2 was considered in addition to current referral (49% vs 58%, P-value <.001). Adjunct KFRE-2 significantly reduced too-early creation (31% vs 18%, P-value <.001).

Conclusions. KFRE in addition to existing eGFR-based referral for VA creation has the potential to improve VA resource utilization by ensuring more patients start HD on AVF/G and may minimize too-early/unnecessary creation. Prospective research is necessary to validate these findings.

Keywords: chronic kidney disease, hemodialysis, KFRE, vascular access

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KEY LEARNING POINTS

What was known:

- In most patients reaching end-stage kidney disease requiring hemodialysis (HD), an arteriovenous fistula/graft (AVF/G) is the preferred type of vascular access (VA).
- Predicting the optimal time of creating the VA is difficult.
- In this population-based, retrospective cohort study, we described the VA creation and utilization pattern under the existing eGFR–based referral, and investigated the utility of Kidney Failure Risk Equation (KFRE) score as an adjunct variable in VA planning.

This study adds:

- The proportion of patients who started HD on AVF/G within 2 years from the modality selection date (timely pre-emptive creation of VA) was 49% for current eGFR-based referral compared with 58% when an adjunct KFRE-2 of >40% was used.
- An adjunct KFRE-2 of >40% appeared to reduce too-early creation of VA, 18% versus 31% for the current referral system.

Potential impact:

- The KFRE as an adjunct variable to the existing eGFR-based referral for VA creation has the potential to improve the overall VA resource utilization.
- More patients may start HD on fistula or graft.
- Fewer patients would have an AVF/G unutilized for an extended period of time.
- Adopting a KFRE threshold to guide the timing of VA creation may be useful in clinical practice.

INTRODUCTION

Patients with advanced chronic kidney disease (CKD) may progress to end-stage kidney disease (ESKD) over time. In most patients reaching ESKD requiring hemodialysis (HD), an arteriovenous fistula/graft (AVF/G) is the preferred type of vascular access (VA) [1, 2]. Predicting the optimal time of creating the VA is difficult [1]. The Canadian Society of Nephrology recommends creating an AVF/G in patients with CKD with eGFR of 15–20 mL/min/1.73 m^2 [1]. Several other guidelines from the UK and North America also suggest initiating VA planning in patients with CKD with eGFR of 15–29 mL/min/1.73 m^2 [1, 3, 4]. However, the eGFR-based predictions of dialysis initiation within 6–12 months appeared to be poor [2].

Previous studies have reported that approximately 45% of patients who had AVF/G created based on eGFR referral did not use it during the follow-up period [2]. Similarly, in a large study including US Veterans, when VA creation was referred based on eGFR <25 mL/min/1.73 m^2, only 33% of VA created were used among younger patients aged <44 years and 17% were used in older patients aged 85–100 years [5]. The uncertainty of the timing of the creation, and subsequent use of AVF/G, may have adverse consequences on patients' quality of life and healthcare resource utilization. A tool to optimize the time of VA creation is therefore needed [1, 2].

The Kidney Failure Risk Equation (KFRE) for predicting the risk of developing kidney failure in patients with CKD Stage 3–5 was first developed in Canada [6] and has been validated in several countries worldwide [7]. Recent research suggests that KFRE can play a better role in VA planning [1, 2]. In British Columbia (BC), Canada, patients with an eGFR between 15 and 20 mL/min/1.73 m^2 who are expected to require dialysis within 12 months are referred for access creation [8]. We hypothesized that VA planning using an adjunct KFRE score estimated on the assessment date would result in more appropriate utilization of AVF/G services compared with the current eGFR-based referral. In this study, our objective was 2-fold: First, we described the eGFR-based referral VA creation and utilization pattern among real-world patients with CKD in BC, Canada. Second, we investigated the utility of the KFRE score as an adjunct variable in VA planning among the same patient population.

MATERIALS AND METHODS

Study population

This retrospective cohort study was conducted using data from the Patient Records and Outcome Management Information System (PROMIS), a population-based integrated registry database for patients with CKD who are under specialized nephrologist care in BC, Canada [9]. Patients with non-dialysis-dependent CKD aged ≥18 years with an eGFR <20 mL/min/1.73 m^2 who had documented choice of HD as their preferred dialysis modality from 1 January 2010 to 31 August 2020 were included. Modality selection date was the index date. Patients with a functional AVF/G on or before the index date were excluded. eGFR and urine albumin–creatinine ratio (UACR) were required to calculate the KFRE score; therefore, patients who did not have at least one eGFR and UACR recorded within index date ±90 days were excluded. Patients who received peritoneal dialysis (PD) anytime during the entire study period were also excluded. Finally, we excluded patients who were residents of outside of BC. This study was approved by the Clinical Research Ethics Board at the University of British Columbia, Canada (H22-03199).

Exposure definition

We calculated the KRFE 2-year risk score (KFRE-2) on the index date using age, sex, eGFR and albuminuria [6]. The KFRE score was calculated during the current analysis, and was not routinely used in VA planning. We used the KFRE-2 score retrospectively as an adjunct variable with the existing eGFR-based referral for VA creation, and we investigated whether compared with the current eGFR-based referral, a new criteria of 'current eGFR-based referral plus KFRE' would further improve the clinical decision making in triggering AVF/G creation. The exposures were categorized as (i) current eGFR-based referral in BC, i.e. 'refer for vascular access creation when the patient's eGFR has decreased to <15–20 mL/min/1.73 m^2 and the patient is expected to require dialysis within 12–18 months' [3, 4, 8, 10], (ii) eGFR-based referral plus KFRE-2 >40% and (iii) eGFR-based referral plus KFRE-2 ≤40%.

Outcome variable

To describe the current eGFR-based referral VA creation and utilization pattern among real-world patients with CKD in BC, Canada, we reported the total number of patients who created AVF/G within 2 years from index date. We then estimated the proportion of patients who started HD on AVF/G within 2 years and median time from index date to HD initiation. We also looked into the number of deaths before HD initiation within 2 years from index date and median time to death.

Efficient utilization of VA resources can occur under two clinical scenarios: (i) patients start HD with a pre-emptively created AVF/G and (ii) avoidance of too-early or unnecessary creation of VA in patients who did yet require HD initiation. In this study, we estimated the proportion of patients who started HD on an AVF/G within 2 years from the index date, indicating timely pre-emptive creation, where a higher proportion would indicate more efficient utilization. A patient was considered to start HD on AVF/G if the first HD was initiated on a working AVF/G. We also estimated the proportion of patients in whom an AVF/G was created, but patient did not start HD within 2 years from the index date, indicating too-early creation of AV access, where a lower proportion would indicate more efficient VA resource utilization.

Co-variables

In the KFRE equation, age in years was entered as a continuous variable and sex was entered as male or female. GFR was estimated in mL/min/1.73 m^2 and entered as a continuous variable. eGFR was recorded as the one closest to the index date ±90 days. If a patient started HD within 90 days from the index date, then eGFR before the first dialysis start was considered. In the PROMIS database, UACR was recorded as mg/mmol. We converted this unit to mg/g by dividing the UACR value by 0.113 before entering this as a continuous variable in the equation. Like eGFR, UACR was also recorded as the one closest to the index date ±90 days and no later than the dialysis start date.

The PROMIS database had missing data on VA creation record. Hence, the indicator variable of AVF/G creation (yes/no) was created as a composite of either having an AVF/G creation record before HD initiation or the patient started HD on a working AVF/G (i.e. the AVF/G must have been created before HD initiation).

We also recorded several covariables to describe the patient characteristics. In addition to age, sex, eGFR and UACR variables used in the KFRE equation, we recorded self-reported race, KFRE-2 score on index date, CKD vintage and etiology, and a few comorbidities at baseline including diabetes, cardiovascular and respiratory diseases. We also reported the baseline history of immunosuppressive (IS) medication use, i.e. dispensation of any IS medication within 90 days before the index date.

Statistical analysis

Descriptive statistics were reported as frequencies and proportion for categorical variables and median [interquartile range (IQR)] for continuous variables.

Study participants were followed prospectively for 2 years from the index date until they started maintenance HD or died before HD initiation or were censored due to emigration, recovered kidney function, kidney transplantation or withdrawal from dialysis, whichever occurred first. We reported the number and proportion and 95% confidence interval (CI) of patients who started HD within 2 years (yes/no) or experienced death before HD initiation. The 95% CI was calculated from the binomial distribution of the proportions. We used 1-sample binomial proportion test to investigate if the proportions of patients in KFRE plus current eGFR-based referral group were statistically significantly superior compared with those in current eGFR-based referral group, considering the current eGFR based performance as null hypothesis. Normal approximation was applied.

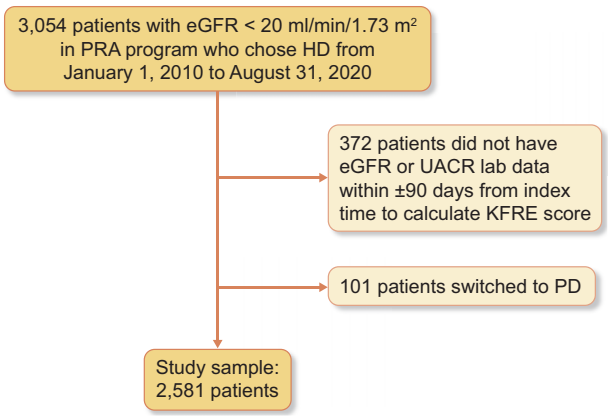

Figure 1: Derivation of study sample from PROMIS registry database. PRA: Provincial Renal Agency.

We re-grouped the study sample based on HD start within 2 years (yes/no) and looked into the differences in key predictors for HD initiation outcome, i.e. age, sex, eGFR, UACR and KFRE-2 score at baseline.

Finally, we compared the utility of KFRE-2 score >40% as an adjunct variable for VA planning by estimating the proportion of patients who started HD on AVF/G within 2 years from the index date.

In a sensitivity analysis, we identified all the patients with CKD who did not start HD within 2 years and followed them for a longer time, until 31 May 2023 and estimated the proportion of patients who eventually started HD or experienced death before HD initiation for overall study sample and by AVF/G creation status (yes/no). In a separate sensitivity analysis, we estimated the proportions by KFRE exposure status. All analyses were conducted using SAS (English) License 9.4.

RESULTS

Study cohort derivation

Between 1 January 2010 and 31 August 2020, 3054 patients registered in PROMIS choose HD as their preferred dialysis modality. eGFR and UACR required for KFRE-2 score calculation was not recorded for 372 patients and they were excluded. A total of 101 patients who switched to PD were also excluded. So, the study sample included 2581 patients with CKD (Fig. 1).

Patient characteristics

Table 1 presents the patient characteristics of the overall study sample and by VA creation status (yes/no). Median age of the study sample was 71 years and 60% were male. Compared with patients in whom a VA was not created, the proportion of males was higher among patients in whom an AVF/G was created, 62% vs 58% (Table 1). The proportion of Asians in the overall study sample was 32%, and the proportion was higher in

Table 1: Patient characteristics by vascular access creation status.

		AVF/G created		
	Overall study sample	Yes	No	*P*-value
N (%)	2581 (100)	1347 (52)	1234 (48)	.1508
Age (years)	71.0 (62.0, 79.0)	70.0 (62.0, 77.0)	72.0 (62.0, 80.0)	
Sex (male), *n* (%)	1548 (60.0)	831 (61.7)	717 (58.1)	.0631
Race, *n* (%)				
Caucasian	1423 (55.1)	746 (55.4)	678 (54.9)	.0016
Oriental Asian	328 (12.7)	198 (14.7)	130 (10.5)	
East-Indian Asian	496 (19.2)	258 (19.2)	237 (19.2)	
Indigenous	82 (3.2)	38 (2.8)	44 (3.6)	
Others	235 (9.1)	101 (7.5)	134 (10.9)	
Missing	17 (0.7)	6 (0.5)	11 (0.9)	
eGFR (mL/min/1.73 m^2) at index	14.0 (12.0, 17.0)	15.0 (12.0, 17.0)	14.0 (11.0, 17.0)	<.0001
UACR (mg/mmol) at index	117.6 (27.7, 301.0)	139.7 (42.7, 316.7)	98.1 (18.5, 282.7)	.0021
KFRE-2 on index	48.9 (25.9, 70.6)	50.0 (30.8, 69.7)	46.8 (21.6, 71.6)	.0215
CKD vintage (year)	2.7 (1.1, 5.1)	2.7 (1.4, 5.1)	2.6 (0.9, 5.1)	.0736
Etiology of kidney disease, *n* (%)				
Diabetic nephropathy	908 (35.2)	505 (37.5)	403 (33.0)	<.0001
Glomerulonephritis	335 (13.0)	176 (13.1)	159 (12.9)	
Polycystic kidney disease	98 (3.8)	67 (4.9)	31 (2.5)	
Others	1240 (48.0)	599 (44.5)	641 (51.9)	
Comorbidities, *n* (%)				
Diabetes	1608 (62.3)	846 (62.8)	762 (61.8)	.5803
CVD-related comorbidities	1399 (54.2)	732 (54.3)	667 (54.1)	.8821
Respiratory disease	669 (25.9)	376 (27.9)	293 (23.7)	.0157
Baseline history of immunosuppressive medication use, *n* (%)	110 (4.3)	40 (3.0)	70 (5.7)	.0006
Started HD within 2 years				
Yes, *n* (%)	1562 (60.5)	935 (69.4)	627 (50.8)	<.0001
No, *n* (%)	1019 (39.5)	412 (30.6)	607 (49.2)	
Median time to initiate HD (days)	198.0 (79.0, 359.0)	267.0 (154.0, 421.0)	76.0 (21.0, 222.0)	<.0001
Median time from index date to AVF/G created				
Overall		106.0 (60.0, 190.0)		
Started HD within 2 years		96.0 (55.0, 168.0)		
Did not start HD within 2 years		139.0 (67.5, 297.0)		

Data are presented as *n* (%) or median (IQR).
CVD: cardiovascular disease.

the VA created group, 34% versus 30%. Median eGFR at baseline was 15 and 14 mL/min/1.73 m^2, respectively. All the patients had moderately increased albuminuria with higher UACR in VA created group (median UACR at baseline was 140 versus 98 mg/mmol) (Table 1). The KFRE-2 score on index date was ~49 for the overall study sample and was higher in the VA created group, 50% versus 47%. Median time between registration in PROMIS and before cohort entry (CKD vintage) was 2.7 years that was comparable between groups. Diabetic nephropathy was the cause of CKD in one in every three patients. Diabetes was the most prevalent comorbidity (62%), more than half had cardiovascular disorders and one in every four patients had respiratory diseases. Exposure to IS medication within 90 days before index date was low (~5%), and the proportion was almost double among patients in whom VA was not created (Table 1).

Description of real-world patient journey from dialysis modality selection date

Figure 2 presents the real-world scenario in progression to kidney failure, i.e. initiation of maintenance HD or death before HD initiation. Out of 2581 patients with CKD who had documented choice of HD as preferred dialysis modality, an AVF/G was created within 2 years from the modality selection date in 1347 (52%) patients. The majority, 1321 of 1347 (98%), of the VA created were AVF, and only 41 patients (3%) had AVG. Median time between index date and the AVF/G creation date was 106 days. On the other hand, an AVF/G was not created in 1234, approximately one in every two patients (~48%) (Fig. 2).

Among 1347 patients in whom an AVF/G was created, 935 (69%) started HD within 2 years, 61 (5%) experienced death before HD initiation within 2 years and 351 (26%) did not start HD within 2 years. Of the 935 patients who started HD, 666 (71%) started on a working AVF/G whereas 269 (29%) started on a central venous catheter (CVC), of whom 187 (70%) ultimately switched to AVF/G within 2 years from the index date (Fig. 2).

Among 1234 patients in whom an AVF/G was not created, 627 (51%) started HD within 2 years, 215 (17%) experienced death before HD initiation within 2 years and 392 (32%) did not start HD within 2 years. In this group, all 627 patients started HD on a CVC, of whom 252 (40%) ultimately switched to AVF/G within 2 years from the index date (Fig. 2).

Combining the results from both arms, in the overall cohort of 2581 patients, 1562 (61%) started HD within 2 years, 276 (11%) experienced death before HD initiation within 2 years and 743 (29%) did not start HD within 2 years. Of the 1562 patients who started HD, only 666 (43%) started on a working AVF/G and 896 (57%) started on a CVC, of whom 439 (49%) switched to AVF/G within 2 years from the index date (Fig. 2). The median time from index date to initiate HD was 198 days for overall study

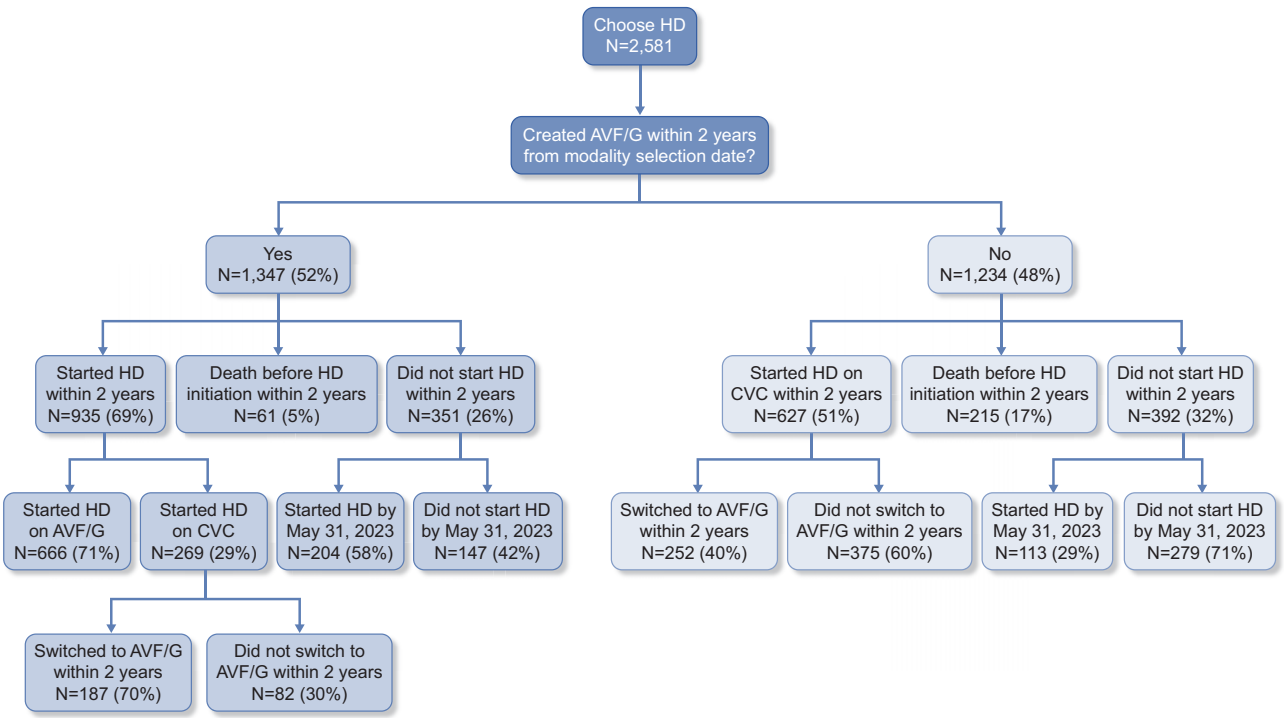

Figure 2: Flow diagram of eGFR-based referral for vascular access creation and initiation of HD among real-world patients with CKD from British Columbia, Canada.

Table 2: Full cohort analysis of the predictors of HD initiation at the time of dialysis modality selection.

		Started HD within 2 years from modality selection date		
Patient characteristic on index date	Overall study Sample 2581 (100%)	Yes, 1562 (61%)	No, 1019 (39%)	*P*-value
Age (years)	71 (62, 79)	70 (59, 77)	73 (65, 81)	<.001
Sex (male), %	60	63	55	.0001
eGFR (mL/min/1.73 m^2)	14 (12, 17)	13 (11, 16)	16 (14, 18)	<.001
UACR (mg/mmol)	118 (28, 301)	201 (71, 396)	43 (11, 131)	<.001
KFRE-2	49 (26,71)	60 (41, 78)	29 (16, 50)	<.001

Data are presented as % or median (IQR).

sample. This median time was substantially shorter among patients in AVF/G not crated group compared with patients in whom an AVF/G was created, 76 and 267 days, respectively (Table 1).

In a sensitivity analysis, we extended the follow up period beyond 2 years from the index date and followed the patients until 31 May 2023. We observed that among 743 patients who did not start HD within 2 years (351 in VA created group and 392 in VA not created group), a total of 317 (43%) started HD by the extended follow up end date.

Factors associated with dialysis initiation within 2 years of modality selection date

Table 2 presents the differences in key variables that were associated with HD initiation. The proportion of males was comparatively higher among patients who started HD at 63% vs 55% among patients who did not start HD (Table 2). Median eGFR (mL/min/1.73 m^2) at baseline appeared to be in CKD stage G4 (eGFR 15–29) for patients who did not start HD and in G5 (eGFR <15) for patients who started HD. Compared with patients who did not start HD, albuminuria was substantially higher among patients who started HD, median UACR was 43 and 201 mg/g, respectively (Table 2). KFRE-2 score on index date was more than double among patients who started HD compared with non-starters, 60% risk vs 29% risk.

KFRE as an adjunct variable in VA planning

Among patients in whom VA was created, compared with current eGFR-based referral, an adjunct KFRE of >40% resulted in significantly higher utilization of the AVF/G. The proportion of patients who started HD on AVF/G (timely pre-emptive creation of VA) was statistically significantly higher when an adjunct KFRE-2 of >40% was added compared with the current eGFR-based referral alone. The proportions (95% CI) were 58% (55%, 62%) and 49% (47%, 52%), respectively with a *P*-value of <.001 (Fig. 3A, Table 3).

Similar to higher utilization, an adjunct KFRE-2 of >40% appeared to significantly reduce too-early creation of VA. For example, 31% (28%, 33%) of patients with an AVF/G created

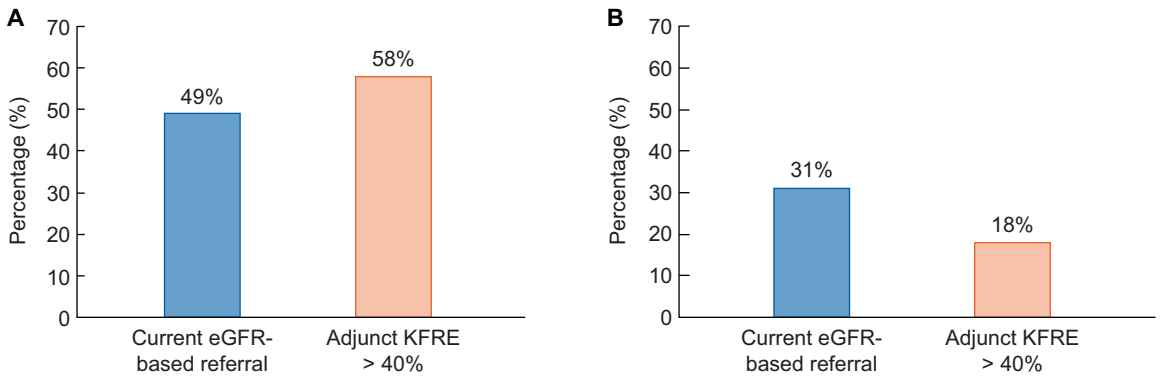

Figure 3: Utility of KFRE as an adjunct variable in VA planning. (A) Patient started HD on AVF/G within 2 years from the modality selection date. (B) An AVF/G was created but patient did not start HD within 2 years from the modality selection date.

Table 3: Comparison of current eGFR-based referral for vascular access creation and eGFR-based referral with adjunct 2-year KFRE.

	Current eGFR-based referral			Current eGFR-based referral + KFRE-2 >40%			Current eGFR-based referral + KFRE-2 ≤40%		
	Overall	AVF/AVG Created	AVF/AVG Not Created	Overall	AVF/AVG Created	AVF/AVG Not Created	Overall	AVF/AVG Created	AVF/AVG Not Created
Number of patients	2581	1347	1234	1552	865	687	1029	482	547
% of patients[a]		52	48		56	44		47	53
Number of patients started HD	1562	935	627	1196	711	485	366	224	142
% of patients started HD[b]	61	69	51	77	82	71	36	46	26
Number of patients started HD on AVF/AVG	666	666		506	506			160	
% of patients started HD on AVF/AVG[b]	43	49		42	58			33	
Number of patients did not start dialysis	1019	412	607	356	154	202	663	258	405
% of patients did not start dialysis[b]	39	31	49	23	18	29	64	54	74

[a] Percentage was calculated with respect to number of patients under the referral scenario irrespective of the status of AVF/AVG creation.
[b]Percentage was calculated with respect to number of patients started dialysis under each combination of referral scenario and AVF/AVG creation status.

based on current eGFR-based referral did not start HD on that AVF/G within 2 years from the index date. An adjunct KFRE-2 of >40% statistically significantly reduced this too-early creation to 18% (0%, 20%), *P*-value <.001 (Fig. 3B, Table 3).

In addition, an adjunct KFRE-2 of ≤40% would have avoided AVF/G creation in 258 patients who did not start HD within 2 years (Table 3). However, an adjunct KFRE of ≤40% might have misclassified 366 out of 2581 [14% (13%, 16%)] patients by not referring for VA creation while in actual practice they started HD within 2 years from the index date (Table 3).

In a sensitivity analysis involving all patients who did not start HD within 2 years, compared with current eGFR-based referral, a greater proportion of patients in the adjunct KFRE-2 >40% group eventually started HD when followed until 31 May 2023, 64% (56%, 71%) versus 54% (50%, 59%), respectively. In another sensitivity analysis, we excluded patients with PKD and patients who received kidney transplantation before the index date ($n = 2454$). Patients characteristics and directionality and magnitude of the proportion of patients who started HD within 2 years were similar to the findings from the primary analyses.

DISCUSSION

In this population-based cohort study of patients with CKD Stages G4–G5 followed by nephrologists in BC, Canada, we found that an AVF/G was created within 2 years from the dialysis modality selection date in only half of the patients who choose HD as their preferred dialysis modality. Approximately 61% of the study sample started HD and 11% experienced death before HD initiation within 2 years. Among all patients who started HD within 2 years, only 43% started HD on a working AVF/G. The remaining 57% started HD on a CVC, of whom 49% eventually switched to AVF/G. A KFRE-2 score of >40% in conjunction with the current eGFR-based referral criteria can improve the use of AVF/G created (58%), as compared with using eGFR thresholds alone (49%). Application of adjunct KFRE-2 of >40% would potentially also have reduced the number of created AVF/G but not used within 2 years (18% vs 31%). Taken together, these findings support the use of a KFRE-2 based threshold of >40% in addition to an eGFR of 15–20 mL/min/1.73 m^2 to trigger the creation of VA.

To the best of our knowledge, this is the first population-level registry data–based study investigating the role of KFRE-2 as an adjunct variable to the existing eGFR-based referral for VA

planning. Our results are consistent with the findings from previous studies that examined the accuracy of the KFRE in patients with advanced CKD. For example, in a retrospective cohort study conducted using health administrative data from Ottawa, Canada, Hundemer *et al*. concluded that KFRE performed well in the calibration and discrimination of the incident kidney failure outcome in patients with eGFR <25 mL/min/1.73 m^2 [11].

In BC, patients are provided with the education about dialysis options when the patient's eGFR is 20–25 mL/min/1.73 m^2 [12]. Patients are expected to select their preferred mode of dialysis at an eGFR of 20 mL/min/1.73 m^2 [12]. Patients are referred for vascular access creation when the patient's eGFR has decreased to <15–20 mL/min/1.73 m^2 and the patient is expected to require dialysis within 12–18 months [8, 10]. This is similar to the 18-month time frame in the UK national guidance for AVF formation [3, 4].

There are increasing data to suggest that KFRE is superior in predicting dialysis within 1–2 years to patients or physicians [13], likely due to individual variability in nephrologist's assessment. In contrast, the KFRE uses individual patient level laboratory data to estimate the risk of progressing to kidney failure in the short-term, is validated in more than 30 countries and is frequently used in estimating the patient's risk [7]. We sought to test the hypothesis that the combination of the eGFR threshold and KFRE threshold would result in more accurate prediction of dialysis start on AVF/G. In a prospective study involving patients with CKD who were referred by nephrologists and were assessed for VA creation, a KFRE-2 cut off of >40% on the date of assessment had a sensitivity of 88% for initiating dialysis within 6 months and 80% for initiating dialysis within 12 months [2]. The sensitivity and specificity of KFRE-2 for initiating HD observed in the current study were similar (results not shown). So, the apparent improvement in AVF/G utilization and avoiding too-early creation of VA with an adjunct KFRE-2 score in VA planning is plausible.

Despite having high sensitivity and performing well in improving the proportion of patients starting HD on AVF/G, the low specificity of KFRE-2 in predicting HD initiation may inaccurately classify some patients as not-referred for AVG/G creation when used as an adjunct to eGFR. In the present analysis, we observed that an adjunct KFRE-2 of ≤40% would not have recommended 366 patients for AVF/G creation who started HD within 2 years. Future research is necessary to understand this patient population better, and to identify the time to dialysis in these patients from the first instance of eGFR <15 mL/min/1.73 m^2 or KFRE >40% in longitudinal follow-up.

Our findings have direct implications for VA planning. For example, an adjunct KFRE-2 of >40% would correctly identify patients with CKD who may start HD on AVF/G within 2 years. This would result in the timely pre-emptive creation of VA in a greater proportion of patients. On the other hand, 258 patients in the adjunct KFRE-2 of ≤40% in whom an AVF/G was created but did not start HD within 2 years would have been correctly classified as not-referred for AVG/G creation. The resources for creating these 258 VA could be redirected to prioritize AVF/G creation with an adjunct KFRE-2 of >40%, and other priority healthcare expenditures. In addition, these patients would avoid any morbidity associated with the fistula surgery which can include nerve damage, steal syndrome and exacerbation of heart failure. From a system perspective, costs of care are also more likely to be reduced.

Our study had several strengths. This is the most extensive population-level study in this research area. Compared with the previous single center–based study involving ~200 patients, the current study included >2500 patients over 10 years. We had access to the individual patient-level clinical data over a long period of time which enabled us to accurately estimate the KFRE-2 score and retrospectively investigate its impact on VA creation and subsequent dialysis initiation. Our study also had a few limitations. The record of AVF/G creation was not entirely captured in the PROMIS registry database. However, the composite definition used in creating the indicator variable for AVF/G created (yes/no) should sufficiently identify all patients in whom a VA was created. In addition, our exclusion of patients who received PD anytime during the entire study period would result in a study sample mimicking the patients with CKD who selected HD modality and potential candidates for AVF/G. It is also worth noting that the number of patients who choose HD as their dialysis modality and who actually start HD with AVF/G depends on many factors other than referral for VA creation. These factors include clinical contraindications to AVG/G creation, surgical wait times, maturation times, staffing (e.g. VA coordinator), primary failure rate of AVF/G and patient preference. However, decision-making around VA creation was cited as a common barrier to patients with CKD initiating dialysis with an AVF [14]. Therefore, this study has important clinical and health economic implications for optimizing AVF/G use. It appeared that creation of AVF may delay the onset of dialysis initiation in patients with advanced CKD [15, 16]. This may partially explain the much longer median time to initiate HD observed among patients in whom an AVF/G was created. This could be a source of bias in a study investigating the effect of VA creation (yes/no) on dialysis initiation. However, in this study we compared the VA referral processes and calculated the proportion of patients who did or did not start HD within 2 years among those who already created an AVF/G. So, the positive effect of AVF on CKD progression was consistent in both exposure groups and may not bias our outcome measures. We included patients into the study on the day the patient chose HD as their mode of dialysis. This enabled us to investigate the natural course of patients' journey in progression to kidney failure. Half of our study sample had a baseline eGFR of 14 mL/min/1.73 m^2, which is somewhat higher than the KDIGO recommended eGFR level of <10 mL/min/1.73 m^2 for dialysis initiation [17]. Future studies could start following up patients at a later index date with a lower baseline eGFR. Currently, patients with CKD in BC may be referred for VA creation from 15 kidney care clinics. Although, all nephrologists working in the province have wide access to BC Renal's standardized protocols for this referral and are expected to follow, differences may still exist in the proportion of patients starting HD within 2 years. Future studies could investigate the between nephrologist/clinic/region level difference in following referral criteria and kidney disease outcomes.

In conclusion, our findings indicate that KFRE-2 cut off of >40% as an adjunct variable to the existing eGFR-based referral for VA creation has the potential to improve the overall VA resource utilization by ensuring more patients start HD on fistula or graft and may minimize too-early or unnecessary creation of AVF/G. Considering the retrospective nature of this observational study, these findings should be interpreted cautiously. The results are hypothesis generating, and future prospective research is necessary to validate the study findings and to develop tools or strategies that will improve the referral for patients with an adjunct KFRE of ≤40%.

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AUTHORS' CONTRIBUTIONS

Study concept: A.L., M.B. and M.A. Statistical analyses: B.Z., A.R., L.E. and O.D. Interpreting results: M.A., B.Z., A.R., L.E., O.D., M.B., M.W., P.B., T.W.Y., A.S., N.T. and A.L. Manuscript writing: M.A. wrote the first draft of the manuscript. All authors critically evaluated the manuscript and provided feedback. M.A. implemented the feedbacks and developed the subsequent versions.

DATA AVAILABILITY STATEMENT

This study was conducted using de-identified health administrative data. Study data can be accessed with approval from the concerned Ethics Board and the data stewards.

CONFLICT OF INTEREST STATEMENT

None from any author.

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