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Development and Validation of Prediction Scores for Early Mortality at Transition to Dialysis

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Abstract

Objective: To develop and validate a risk prediction model that would help individualize treatment and improve the shared decision-making process between clinicians and patients.

Patients and Methods: We developed a risk prediction tool for mortality during the first year of dialysis based on pre-end-stage renal disease characteristics in a cohort of 35,878 US veterans with incident end-stage renal disease who transitioned to dialysis treatment between October 1, 2007, and March 31, 2014 and then externally validated this tool among 4284 patients in the Kaiser Permanente Southern California (KPSC) health care system who transitioned to dialysis treatment between January 1, 2007, and September 30, 2015.

Results: To ensure model goodness of fit, 2 separate models were selected for patients whose last estimated glomerular filtration rate (eGFR) before dialysis initiation was less than 15 mL/min per 1.73 m² or 15 mL/min per 1.73 m² or higher. Model discrimination in the internal validation cohort of veterans resulted in C statistics of 0.71 (95% CI, 0.70-0.72) and 0.66 (95% CI, 0.65-0.67) among patients with eGFR lower than 15 mL/min per 1.73 m² and 15 mL/min per 1.73 m² or higher, respectively. In the KPSC external validation cohort, the developed risk score exhibited C statistics of 0.77 (95% CI, 0.74-0.79) in men and 0.74 (95% CI, 0.71-0.76) in women with eGFR lower than 15 mL/min per 1.73 m² and 0.71 (95% CI, 0.67-0.74) in men and 0.67 (95% CI, 0.62-0.72) in women with eGFR of 15 mL/min per 1.73 m² or higher.

Conclusion: A new risk prediction tool for mortality during the first year after transition to dialysis (available at www.DialysisScore.com) was developed in the large national Veterans Affairs cohort and validated with good performance in the racially, ethnically, and gender diverse KPSC cohort. This risk prediction tool will help identify high-risk populations and guide management strategies at the transition to dialysis.

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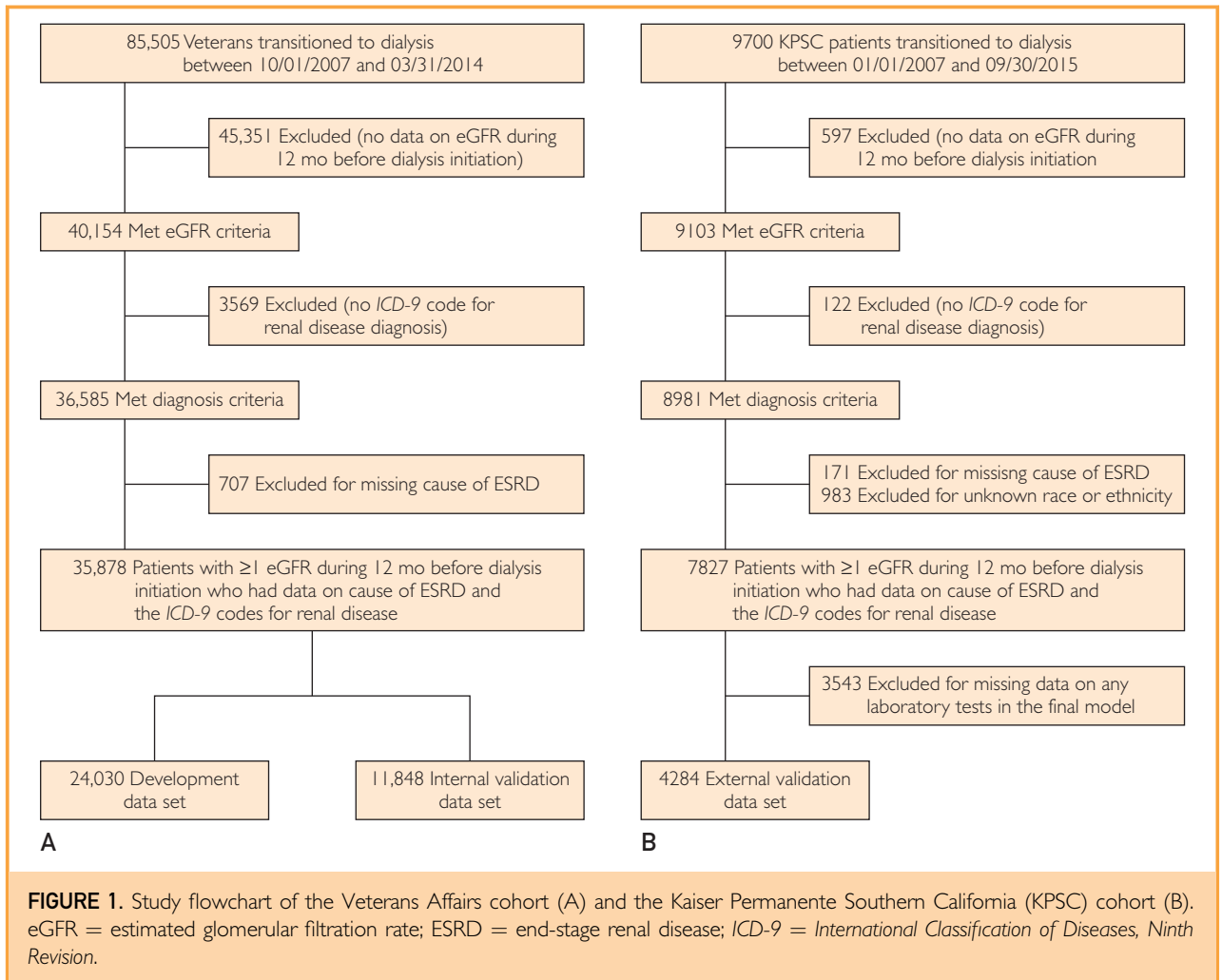
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The number of incident cases of end-stage renal disease (ESRD) in the United States has risen over time and exceeded 120,000 in 2014.¹ There is substantial heterogeneity in the incident ESRD population in which some patients may die early after dialysis initiation while others may experience greater longevity with dialysis. Overall, mortality is exceptionally high during the first year of dialysis.¹

Plans for the initiation of maintenance dialysis therapy, including whether to initiate

dialysis, integrate conservative care, or organize end-of-life support, are affected by various factors such as comorbid conditions, personal beliefs, and cultural perspectives.^{2,3} A risk prediction model to predict early mortality could help individualize treatment and support the shared decision-making process among clinicians, patients, and patients' family members. For example, if a patient has high anticipated risk of mortality within 1 year of dialysis, conservative management with infrequent dialysis therapy could be a potential



option.⁴⁻⁶ Additionally, it may provide little or no benefit but rather harm in such a case to provide aggressive treatments for cancer or certain chronic conditions such as hypertension, atrial fibrillation, or hyperphosphatemia.

Several prediction models have been developed for patients among whom the decision to implement dialysis has been already made.⁷⁻¹⁶ However, most of the previous models utilized data obtained at the time of or after dialysis initiation⁸⁻¹⁶ despite the fact that the shared decision-making process regarding dialysis initiation would sometimes require several weeks. Other limitations of prior models include small sample sizes,⁷⁻⁹ restriction of study populations to those of elderly age,^{7,10-12} the use of less contemporary cohorts (before 2005),^{8,9,12-14} lack of information on race and/or ethnicity,^{7-9,11,12,16} and nonconsideration of readily available laboratory data

such as serum albumin and/or estimated glomerular filtration rate (eGFR).^{7-9,11-16} Additionally, model performance was not externally validated in most cases.^{7-13,15}

The aim of this study was to develop, rigorously validate, and provide risk scores to predict mortality during the first year of dialysis (ie, months 3, 6, 9, and 12) based on pre-ESRD information among patients who would transition to dialysis.

PATIENTS AND METHODS

Study Population and Data Source

The Transition of Care in Chronic Kidney Disease study included 2 historical cohorts with incident ESRD: (1) 85,505 US veterans who transitioned to dialysis treatment from October 1, 2007, through March 31, 2014,¹⁷⁻²⁰ and (2) 9700

patients who transitioned to dialysis within the Kaiser Permanente Southern California (KPSC) health care system from January 1, 2007, through September 30, 2015, both derived from the United States Renal Data System (USRDS). In the current study, we excluded patients without data on eGFR during the 12 months before dialysis initiation, those without the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes for renal disease, those with missing cause of ESRD, or unknown race/ethnicity (Figure 1, A). We further restricted patients in the KPSC cohort to those without missing data on the variables selected in the final model (Figure 1, B). Differences in characteristics between included vs excluded patients for each cohort are summarized in Supplemental Tables 1 and 2 (available online at <http://www.mayoclinicproceedings.org>). This study was approved by the institutional review boards of the Memphis, Tennessee, and Long Beach, California, Veterans Affairs (VA) Medical Centers and KPSC. The requirement for written informed consent was waived because of the large sample size, patient anonymity, and noninvasive nature of the study.

Demographic Characteristics, Clinical Data, and Laboratory Measurements

Baseline patient characteristics were drawn from a composite of USRDS Patient and Medical Evidence files, Centers for Medicare and Medicaid Services (CMS) databases, and the respective administrative databases (ie, either the VA or KPSC). Cause of ESRD was categorized into 8 groups based on the *ICD-9-CM* diagnosis codes indicated in the Medical Evidence Report form CMS-2728 (Supplemental Table 3, available online at <http://www.mayoclinicproceedings.org>). We defined pre-ESRD comorbidity status by the *ICD-9-CM* diagnosis and surgical codes recorded in both CMS and administrative databases (Supplemental Table 4, available online at <http://www.mayoclinicproceedings.org>). Additionally, all patients with diabetes as the cause of ESRD were considered to have diabetes with complications. For comorbidities with 2 levels (ie, diabetes [with vs without complication], liver disease [mild vs moderate or severe], and cancer [nonmetastatic vs metastatic]), patients were considered to have only the more severe condition if they had both

comorbidities. Ischemic heart disease included myocardial infarction.

All data on body mass index and laboratory tests were obtained before dialysis initiation. We calculated eGFR using the Chronic Kidney Disease Epidemiology Collaboration formula.²¹ The last measurement of each variable before ESRD transition was used in this study.

Statistical Analyses

Differences between groups were compared by standardized differences because of the large sample size of this study.^{22,23} Differences in patient characteristics between 2 groups were compared by standardized difference, of which 0.8, 0.5, and 0.2 in absolute value were considered large, medium, and small differences, respectively.

Prediction models for mortality during the first year of dialysis were developed on the basis of survival data up to 14 months after transition to dialysis using Cox proportional hazards models. Follow-up started at dialysis initiation and continued until death or the date of final follow-up assessment (September 2, 2014). Information on date of censoring events was obtained from the records of the CMS, USRDS, and respective administrative database. As candidate predictors, we a priori selected clinically relevant variables less likely to be intentionally modified (Table 1) and excluded medications and easily modifiable variables (ie, hemoglobin, potassium, calcium, phosphorus, intact parathyroid hormone, bicarbonate, ferritin, and lipids). The proportions of missing data were approximately 3% for body mass index, serum sodium, and serum urea nitrogen and approximately 10% for white blood cell, serum albumin, and serum alkaline phosphatase. Missing data in the VA cohort were imputed by their mean values.

The VA cohort was randomly divided into a two-thirds development set (n = 24,030) and a one-third internal validation set (n = 11,848). Final models with reduced number of predictors were obtained in the development data set using backward selection based on Akaike information criterion. To address potential model overfitting (optimism), we estimated a linear shrinkage factor (γ) using 100 bootstrap samples²⁴⁻²⁶ and adjusted the risk score by the

TABLE 1. Pre-ESRD Characteristics of 35,878 Veterans Who Transitioned to Dialysis Therapy From October 1, 2007, through March 31, 2014, Stratified by Last eGFR Measurement Before Dialysis Initiation^{a,b,c}

Candidate predictors	Missing frequency (%)	Total cohort (N=35,878)	Last eGFR (mL/min/1.73 m ²)		Standardized difference ^d
			<15 (n=22,605 [63%])	≥15 (n=13,273 [37%])	
Age (y)	0	69.4±11.1	67.8±11.2	72.2±10.4	-0.41
Male	0	35,215 (98)	22,111 (98)	13,104 (99)	-0.07
Race	0				
White		24,344 (68)	14,123 (62)	10,221 (77)	-0.32
Black		9913 (28)	7323 (32)	2590 (20)	0.30
Native American		204 (0.6)	145 (0.6)	59 (0.4)	0.03
Asian		196 (0.5)	135 (0.6)	61 (0.5)	0.02
Other		1221 (3)	879 (4)	342 (3)	0.07
Hispanic ethnicity	0	2474 (7)	1796 (8)	678 (5)	0.12
Cause of ESRD	0				
Diabetes		17,182 (48)	11,098 (49)	6084 (46)	0.07
Hypertension/large-vessel disease		10,847 (30)	6791 (30)	4056 (31)	-0.01
Primary glomerulonephritis		1766 (5)	1360 (6)	406 (3)	0.14
Interstitial nephritis/pyelonephritis		919 (3)	588 (3)	331 (2)	0.01
Neoplasms/tumors		886 (2)	478 (2)	408 (3)	-0.06
Cystic/hereditary/congenital diseases		582 (2)	468 (2)	114 (0.9)	0.10
Secondary glomerulonephritis/vasculitis		295 (0.8)	189 (0.8)	106 (0.8)	0.00
Miscellaneous conditions		3401 (9)	1633 (7)	1768 (13)	-0.20
Comorbidities (ICD-9-CM)	0				
Renal disease		35,878 (100)	22,605 (100)	13,273 (100)	0.00
Hypertension		35,231 (98)	22,167 (98)	13,064 (98)	-0.03
Hyperlipidemia		29,416 (82)	17,852 (79)	11,564 (87)	-0.22
Anemia		26,481 (74)	16,404 (73)	10,077 (76)	-0.08
Diabetes without complications		6577 (18)	4019 (18)	2558 (19)	-0.04
Diabetes with complications		18,980 (53)	11,694 (52)	7286 (55)	-0.06
Ischemic heart disease		21,234 (59)	11,527 (51)	9707 (73)	-0.47
Myocardial infarction		9397 (26)	4491 (20)	4906 (37)	-0.39
Congestive heart failure		19,870 (55)	10,462 (46)	9408 (71)	-0.52
Atrial fibrillation		5733 (16)	2530 (11)	3203 (24)	-0.34
Peripheral vascular disease		13,773 (38)	7291 (32)	6482 (49)	-0.34
Cerebrovascular disease		11,197 (31)	6088 (27)	5109 (38)	-0.25
Depression		8980 (25)	5615 (25)	3365 (25)	-0.01
Dementia		837 (2)	437 (2)	400 (3)	-0.07
Chronic pulmonary disease		14,973 (42)	7653 (34)	7320 (55)	-0.44
Mild liver disease		3128 (9)	1888 (8)	1240 (9)	-0.03
Moderate or severe liver disease		776 (2)	330 (1)	446 (3)	-0.12
Nonmetastatic cancer		7510 (21)	4367 (19)	3143 (24)	-0.11
Metastatic carcinoma		806 (2)	379 (2)	427 (3)	-0.10
Peptic ulcer disease		2363 (7)	1199 (5)	1164 (9)	-0.14
Connective tissue disease/rheumatic disease		1345 (4)	677 (3)	668 (5)	-0.10
Paraplegia/hemiplegia		1116 (3)	592 (3)	524 (4)	-0.07
HIV/AIDS		361 (1)	267 (1)	94 (0.7)	0.05
Body mass index (kg/m ²)	3	29.9±6.7	29.7±6.5	30.1±6.9	-0.07
Last eGFR (mL/min/1.73 m ²)	0	12.4 (8.6-18.6)	9.5 (7.2-11.9)	21.9 (17.6-30.7)	-2.58
Laboratory tests					
White blood cells (×10 ³ /μL)	9	7.3 (5.9-9.0)	7.3 (5.9-9.1)	7.2 (5.8-8.9)	0.05
Serum sodium (mEq/L)	2	139.1±3.7	138.9±3.8	139.3±3.5	-0.10
Serum albumin (g/dL)	9	3.4±0.6	3.3±0.6	3.5±0.6	-0.21

Continued on next page

TABLE 1. Continued

Candidate predictors	Missing frequency (%)	Total cohort (N=35,878)	Last eGFR (mL/min/1.73 m ²)		Standardized difference ^d
			<15 (n=22,605 [63%])	≥15 (n=13,273 [37%])	
Laboratory tests, continued					
Serum urea nitrogen (mg/dL)	4	65±29	75±27	48±23	1.09
Serum alkaline phosphatase (IU/L)	11	82 (64-108)	80 (63-105)	86 (67-115)	-0.19

^aeGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HIV = human immunodeficiency virus; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; IQR = interquartile range.

^bValues are presented as mean ± SD, median (IQR), or No. (percentage). Percentages may not total 100 because of rounding.

^cSI conversion factors: To convert white blood cell values to ×10⁹/L, multiply by 0.001; to convert sodium values to mmol/L, multiply by 1.0; to convert albumin values to g/dL, multiply by 10; to convert urea nitrogen values to mmol/L, multiply by 0.357; to convert alkaline phosphatase values to μkat/L, multiply by 0.0167.

^dDifferences in patient characteristics between 2 groups were compared by standardized difference, of which 0.8, 0.5, and 0.2 in absolute value were considered large, medium, and small differences, respectively.

shrinkage factor. Overfitting, particularly in small data sets, results in regression coefficients being overestimated (overfitted) for prediction. Thus, a shrinkage factor ($0 \leq \gamma \leq 1$) is estimated and applied to the risk score to shrink the regression coefficients towards zero so that predictions will more likely show better calibration on new patients (ie, validation data). Furthermore, our study has 2 additional protections against overfitting, ie, internal and external validation cohorts.

Model calibration was assessed by calibration plots and a group-based goodness-of-fit test for survival model.²⁷ In both the internal and external validation data sets, model predictive discrimination was assessed using the index of concordance, or C statistic.²⁵

The final prediction models based on the shrunken prognostic score (PS) can be used to estimate the predicted probabilities of all-cause death at a given time t (month). That is, the shrunken PS* that will be used to predict the outcomes of new/future patients will be $PS^* = \gamma \times \beta$, where β is the collection of estimated coefficients in the final prediction model. The predicted survival at time t for a new patient can be obtained as $S_0(t)^{\exp(PS^*)}$, where $S_0(t)$ is the baseline survival estimate from the final model. Kaplan-Meier survival estimates were compared with predicted mortality at months 3, 6, 9, and 12 across 5 risk score categories based on cutoff points at 5th, 35th, 65th, and 95th percentiles in respective eGFR groups of the internal validation cohort. However, predicted survival rates and their 95% CIs were not provided for the external validation

cohort due to data confidentiality because it required merging of the VA and KPSC data at the individual level.

Analyses were performed in SAS version 9.3 PROC PHREG (SAS Institute) and R version 3.12 (R Project for Statistical Computing) using libraries RMS and SURVIVAL.

RESULTS

Baseline Characteristics of the VA Cohort

The 35,878 patients in the VA cohort had a mean (SD) age of 69.4±11.1 years, 35,215 (98%) were male, 24,344 (68%) were white, 2474 (7%) were Hispanic, and 17,182 (48%) had diabetes as the cause of their ESRD (Table 1). The last eGFR before dialysis initiation was 12.4 mL/min per 1.73 m² (interquartile range [IQR], 8.6-18.6 mL/min per 1.73 m²), and the prevalence of low and high eGFR (ie, <15 or ≥15 mL/min per 1.73 m²) were 63% (n=22,605) and 37% (n=13,273), respectively. When compared with patients with low eGFR, those with high eGFR were older, more likely to be white, and more likely to have a history of hyperlipidemia, cardiovascular disease, and chronic pulmonary disease (absolute standardized difference, >0.2). There were no meaningful differences between the development and internal validation data sets (Supplemental Table 5, available online at <http://www.mayoclinicproceedings.org>). The time from the last eGFR measurement to dialysis initiation was 24 days (IQR, 3-109 days). The prevalence of hemodialysis and peritoneal dialysis as the initial dialysis modality was 94% (11,162) and 5% (579),

respectively, and dialysis modality was uncertain among 107 patients (1%). There were a total of 9813 deaths (4525 and 5288 deaths among patients with low and high eGFR, respectively) during the median follow-up of 14 months (IQR, 9-14 months). Six-month and 1-year mortality rates were 10% and 18% among patients with low eGFR, respectively, and 25% and 37% among patients with high eGFR, respectively.

Development of the Prediction Score

A single prediction score resulted in poor model fit ($P < .001$ for goodness-of-fit test). We then evaluated model fit by stratifying patients according to age, race, diabetes as the cause of ESRD, initial dialysis modality, and time from the last eGFR measurement to dialysis initiation, and only stratification based on the last eGFR resulted in significant improvement ($P > .1$ for goodness-of-fit test) (Supplemental Table 6, available online at <http://www.mayoclinicproceedings.org>). This led to the development of 2 separate prediction scores for patients stratified by low and high eGFR. The final early mortality prediction model coefficients are presented in Table 2. The performances of our reduced/simplified models as quantified by C statistics were practically the same as the full models (data not shown).

Supplemental Figure 1, A and B (available online at <http://www.mayoclinicproceedings.org>) shows the predicted probability of 1-year mortality after transitioning to dialysis as a function of risk score (ie, risk plots). Calibration plots comparing observed vs predicted 1-year survival graphically exhibited consistent results (Supplemental Figure 2, A and B, available online at <http://www.mayoclinicproceedings.org>). We also compared Kaplan-Meier estimates and predicted survival at months 3, 6, 9, and 12 after dialysis initiation across 5 categories with cutoff points at 5th, 35th, 65th, and 95th percentiles of risk score in respective eGFR groups (Figure 2, A and B). Predicted survival was slightly lower than actual in the lowest-risk group but was otherwise consistent (well calibrated) with the observed survival.

Internal Validation Within the VA Cohort

The performance of the prediction score was tested in the internal validation data set of

11,848 veterans. The model discrimination was acceptable among patients with low eGFR, with a C statistic of 0.71 (95% CI, 0.70-0.72). The prediction model showed a C statistic of 0.66 (95% CI, 0.65-0.67) among those with high eGFR. Subgroup analyses including initial dialysis modality (ie, hemodialysis vs peritoneal dialysis) showed consistent C statistics except for patients aged 65 years or older, in whom C statistics were 0.66 (95% CI, 0.65-0.68) and 0.63 (95% CI, 0.61-0.64) for those with low and high eGFR, respectively (Table 3). Risk plots are shown in Supplemental Figure 1, C and D.

The group-based goodness-of-fit tests showed no significant difference between observed and predicted 1-year mortality after transitioning to dialysis in both the low and high eGFR groups (overall $P > .1$) (Supplemental Table 6). Calibration plots exhibited consistent results (Supplemental Figure 2, C and D). Predicted vs observed Kaplan-Meier estimates were also consistent, as were those in the development cohort (Figure 2, C and D).

External Validation

Compared with the VA cohort ($n = 35,8780$), the KPSC cohort ($n = 4284$) was younger (65 ± 14 years vs 69 ± 11 years) and included more women (43% [1842] vs 2% [663]), more Asians (11% [487] vs 0.5% [196]), and more Hispanics (30% [1298] vs 7% [2474]) (Supplemental Table 7, available online at <http://www.mayoclinicproceedings.org>). The last eGFR before dialysis initiation in the KPSC cohort was 10.5 mL/min per 1.73 m² (IQR, 7.7-14.1 mL/min per 1.73 m²), and the prevalence of low and high eGFR (< 15 or ≥ 15 mL/min per 1.73 m²) was 79% (3363) and 21% (921), respectively. Time from the last eGFR measurement to dialysis initiation was 11 days (IQR, 5-25 days), and the prevalence of hemodialysis and peritoneal dialysis as the initial dialysis modality was 87% (3727) and 13% (557), respectively. Supplemental Table 8 summarizes data on predictors in the final model stratifying KPSC patients by sex and last eGFR before dialysis initiation. There were a total of 824 deaths (552 and 272 deaths among patients with low and high eGFR, respectively) during the median follow-up time of 14 months (IQR,

TABLE 2. Cox Regression Model for Predicting Mortality Among Patients With Low and High eGFR at the Last Measurement Before Dialysis Initiation^a

Variable	Last eGFR					
	Low (<15 mL/min/1.73 m ²)			High (≥15 mL/min/1.73 m ²)		
	Parameter ^b	HR (95% CI)	P value	Parameter ^b	HR (95% CI)	P value
Age (per year)	0.0311	1.03 (1.03-1.04)	<.001	0.0343	1.03 (1.03-1.04)	<.001
Race						
White		Reference			Reference	
Black	−0.4019	0.67 (0.61-0.73)	<.001	−0.2178	0.80 (0.73-0.89)	<.001
Asian	−0.6334	0.53 (0.29-0.96)	.04	−0.8342	0.43 (0.23-0.81)	.009
Native American	−0.4859	0.61 (0.36-1.04)	.07	−0.6384	0.53 (0.27-1.02)	.06
Other	−0.3692	0.69 (0.55-0.87)	.002	−0.2437	0.78 (0.60-1.02)	.07
Hispanic ethnicity	−0.2926	0.75 (0.64-0.87)	<.001	−0.2547	0.78 (0.64-0.93)	.007
Cause of ESRD						
Diabetes	0.3607	1.43 (1.18-1.74)	<.001	0.3493	1.42 (1.12-1.79)	.003
Hypertension/large-vessel disease	0.4261	1.53 (1.26-1.87)	<.001	0.3428	1.41 (1.11-1.78)	.004
Primary glomerulonephritis		Reference			Reference	
Interstitial nephritis/pyelonephritis	0.5392	1.71 (1.30-2.26)	<.001	0.5632	1.76 (1.30-2.37)	<.001
Neoplasms/tumors	0.8410	2.32 (1.78-3.01)	<.001	0.4618	1.59 (1.18-2.13)	.002
Cystic/hereditary/congenital diseases	−0.0997	0.91 (0.59-1.40)	.66	−0.5306	0.59 (0.32-1.08)	.09
Secondary glomerulonephritis/vasculitis	0.3890	1.48 (0.97-2.25)	.07	0.3876	1.47 (0.95-2.27)	.08
Miscellaneous conditions	0.7526	2.12 (1.71-2.63)	<.001	0.4874	1.63 (1.28-2.07)	<.001
Comorbidities						
Hyperlipidemia	−0.1485	0.86 (0.78-0.95)	.002	−0.1886	0.83 (0.74-0.92)	.001
Diabetes without complications		Not selected		0.1191	1.13 (1.04-1.22)	.004
Ischemic heart disease		Not selected		0.1912	1.21 (1.10-1.33)	<.001
Myocardial infarction	0.1555	1.17 (1.07-1.27)	<.001		Not selected	
Congestive heart failure	0.2273	1.25 (1.16-1.36)	<.001	0.2353	1.27 (1.15-1.39)	<.001
Atrial fibrillation	0.2013	1.22 (1.11-1.35)	<.001	0.1835	1.20 (1.11-1.30)	<.001
Peripheral vascular disease	0.1251	1.13 (1.05-1.23)	.002		Not selected	
Cerebrovascular disease	0.1727	1.19 (1.10-1.29)	<.001	0.1035	1.11 (1.03-1.19)	.004
Dementia	0.4246	1.53 (1.27-1.85)	<.001		Not selected	
Chronic pulmonary disease	0.1796	1.20 (1.11-1.29)	<.001	0.1482	1.16 (1.08-1.25)	<.001
Moderate or severe liver disease	0.7509	2.12 (1.70-2.64)	<.001	0.5212	1.68 (1.44-1.97)	<.001
Metastatic carcinoma	0.7012	2.02 (1.68-2.43)	<.001	0.2675	1.31 (1.12-1.53)	.001
Body mass index (per kg/m ²) ^c	−0.0304	0.97 (0.96-0.98)	<.001	−0.0233	0.98 (0.97-0.98)	<.001
Last eGFR (per mL/min/1.73 m ²) ^c	0.0308	1.03 (1.02-1.05)	<.001	0.0163	1.02 (1.01-1.02)	<.001
Laboratory tests						
White blood cells (per ×10 ³ /μL)	0.0269	1.03 (1.02-1.04)	<.001		Not selected	
Serum albumin (per g/dL)	−0.4381	0.65 (0.61-0.68)	<.001	−0.2610	0.77 (0.73-0.82)	<.001
Serum urea nitrogen (per mg/dL)	0.0025	1.00 (1.00-1.00)	.001	0.0057	1.01 (1.00-1.01)	<.001
Serum sodium (per mEq/L)	−0.0327	0.97 (0.96-0.98)	<.001	−0.0331	0.97 (0.96-0.98)	<.001
Serum alkaline phosphatase (per IU/L)	0.0010	1.00 (1.00-1.00)	<.001	0.0012	1.00 (1.00-1.00)	<.001

^aeGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HR = hazard ratio.

^bModel parameter estimate before application of shrinkage factor (ie, 0.970 and 0.965 for low and high eGFR groups, respectively). Estimated 1-year survival probabilities can be obtained as: $1 - S_0^{e^{(PS^*)}}$, where $PS^* = \gamma \times LP$, γ is the shrinkage factor, LP is the linear predictor using the given parameter estimates, and $S_0(t)$. $S_0(t)$ is the baseline survival estimate from the final model. S_0 at months 3, 6, 9, and 12 were 0.9722, 0.9446, 0.9234, and 0.9011 for patients with last eGFR <15 mL/min/1.73 m², respectively, and 0.9313, 0.8790, 0.8369, and 0.7994 for patients with last eGFR ≥15 mL/min/1.73 m², respectively.

^cLast available value during 1 year before dialysis initiation.

14-14 months). Six-month and 1-year mortality were 9% and 15% among patients with low eGFR, respectively, and 20% and 29% among patients with high eGFR, respectively.

Risk plots for the KPSC cohort show the same pattern of relationship between mortality

and risk score (Supplemental Figure 1, E and F). However, observed survival was typically higher than model-predicted survival, especially in the high-risk groups (Supplemental Figure 2, E and F). Nevertheless, the Kaplan-Meier estimates (Figure 2, E

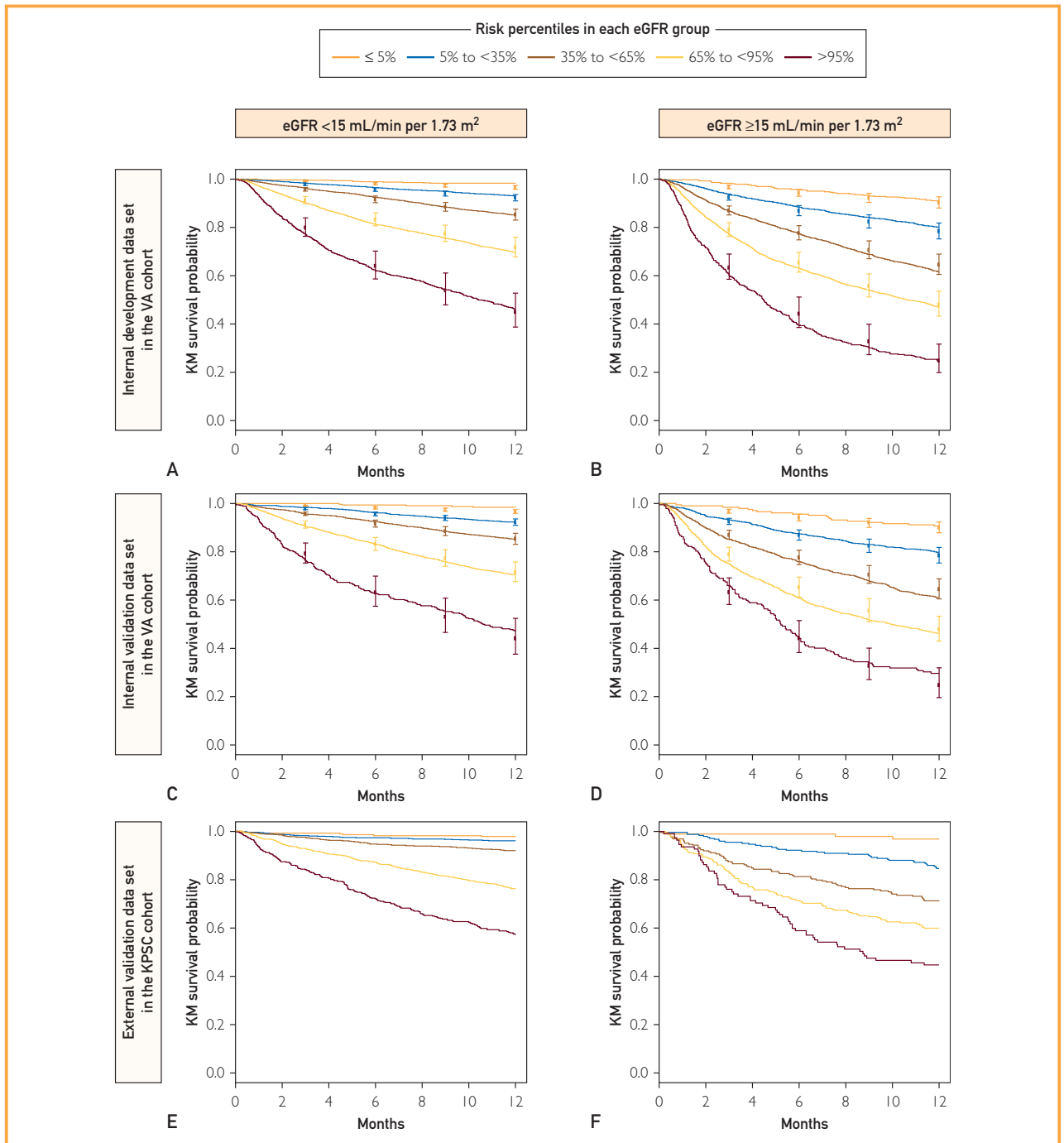


FIGURE 2. Observed survival curves during the first year of dialysis and predicted survival at months 3, 6, 9, and 12 across 5 risk score categories in patients with last estimated glomerular filtration rate (eGFR) before initiation of dialysis of less than 15 mL/min per 1.73 m² or 15 mL/min per 1.73 m² or greater in the development Veterans Affairs (VA) cohort (A and B), the internal validation VA cohort (C and D), and the external validation Kaiser Permanente Southern California (KPSC) cohort (E and F), respectively. Survival curves (solid lines) were based on Kaplan-Meier (KM) estimates. Points and bars represent means and 95% CIs of predicted survival for the risk score categories. Cutoff points were selected at 5th, 35th, 65th, and 95th percentiles in respective eGFR groups of the internal validation cohort and were consistent across cohorts. Predicted survival rates and their 95% CIs were not provided for the external validation cohort due to data confidentiality because it requires merging of the VA and KPSC data at the individual level.

TABLE 3. Overall and Subgroup Analyses of Discrimination Performance as Quantified by C Statistics in the 11,848 Patients in the Internal Validation Veterans Affairs Cohort^a

Subgroup	Last eGFR <15 mL/min/1.73 m ²		Last eGFR ≥15 mL/min/1.73 m ²	
	No. of patients	Median (95% CI)	No. of patients	Median (95% CI)
Overall	7463	0.71 (0.70-0.72)	4385	0.66 (0.65-0.67)
Age (y)				
<65	3317	0.70 (0.68-0.73)	1209	0.69 (0.66-0.72)
≥65	4146	0.66 (0.65-0.68)	3176	0.63 (0.61-0.64)
Race				
White	4697	0.69 (0.67-0.70)	3375	0.64 (0.63-0.66)
Other	2766	0.71 (0.68-0.73)	1010	0.69 (0.67-0.72)
Cause of ESRD				
Diabetes	3677	0.70 (0.68-0.72)	2031	0.68 (0.66-0.70)
Hypertension	2202	0.71 (0.69-0.73)	1338	0.64 (0.62-0.66)
GN/CKD/IN/PN	810	0.70 (0.66-0.74)	260	0.68 (0.63-0.73)
Other	774	0.69 (0.66-0.73)	756	0.62 (0.59-0.65)
Initial dialysis modality ^b				
Hemodialysis	6977	0.71 (0.69-0.72)	4185	0.66 (0.64-0.67)
Peritoneal dialysis	421	0.74 (0.67-0.80)	158	0.72 (0.65-0.79)
Time from last visit to dialysis initiation (mo)				
<6	7098	0.71 (0.69-0.72)	3276	0.66 (0.65-0.68)
6-12	365	0.70 (0.65-0.75)	1109	0.66 (0.63-0.68)

^aeGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; GN = glomerular nephritis; CKD = cystic kidney disease; IN = interstitial nephritis; PN = pyelonephritis.

^bInitial dialysis modality was uncertain among 65 and 42 patients with last eGFR <15 and ≥15 mL/min/1.73m², respectively, and they were excluded in the subgroup analyses based on initial dialysis modality due to small sample sizes.

and F) show the same consistent ordering of survival and risk score percentile (ie, high risk score, high mortality), and the prediction score showed similar or even better discrimination in the KPSC cohort than in the VA cohort; C statistics were 0.77 (95% CI, 0.74-0.79) and 0.74 (95% CI, 0.71-0.76) among men and women with low eGFR, respectively, and 0.71 (95% CI, 0.67-0.74) and 0.67 (95% CI, 0.62-0.72) among men and women with high eGFR, respectively.

DISCUSSION

In this study, we developed a prediction tool for mortality during the first year of dialysis based on pre-ESRD data in a large contemporary national cohort of US veterans. Although the VA cohort has inherently unique characteristics compared with other populations, these new risk scores appeared generalizable given that these were externally validated in the racially, ethnically, and gender diverse KPSC cohort with reasonable discrimination in most studies groups. In order to facilitate practical implementation, we have created an online risk score calculator at www.DialysisScore.com that

provides the predicted risk of mortality at months 3, 6, 9, and 12 after dialysis initiation.

The discriminatory performance of our risk score may be improved by adding other factors such as socioeconomic status,²⁸ medication adherence,²⁹ and timing of referral to nephrologists.^{30,31} In particular, physical and cognitive function may play an important role in predicting outcomes among elderly patients, in whom our risk score showed C statistics of less than 0.7. Indeed, geriatric syndromes such as cognitive impairment and frailty are prevalent in the dialysis population,³² and the decline in cognitive and physical function has been shown to accelerate after dialysis initiation, especially among elderly patients.³³⁻³⁵ These variables are difficult to capture because trained personnel and careful consideration are necessary for their evaluation, but comprehensive risk models accounting for additional measures specific to the elderly population may help predict mortality more precisely.

Several previous prediction models focused on the elderly population^{7,10-12} given the differences in clinical consequences (eg, high mortality and hospitalization rates) and patient

characteristics (eg, more severe comorbid conditions and dialysis initiation with higher eGFR) among older patients.^{36,37} However, we obtained satisfactory model fit with stratification by last eGFR before dialysis initiation but not with stratification by age (data not shown), suggesting that the association between risk factors and outcomes is dependent on comorbid conditions rather than age. Higher eGFR may reflect unmeasured clinical conditions at the time of dialysis initiation, such as severely impaired cardiac function requiring more strict fluid management than usual and overestimation of actual kidney function due to low muscle mass. Indeed, the increased mortality risk associated with higher eGFR in our study was consistent with that in previous studies,⁷ and these heterogeneous conditions may explain why model fit was improved by stratification according to last eGFR and why we observed lower C statistics among patients with high eGFR.

The patterns of mortality during the first year of dialysis have been reported to differ by age and treatment modality.¹ For patients undergoing hemodialysis, mortality is especially high during the first several months, and this early mortality is more remarkable among older patients. In contrast, patients undergoing peritoneal dialysis have relatively constant mortality over the course of the year. Nevertheless, a previous study reported similar outcomes between dialysis modalities when accounting for patient characteristics,³⁸ and our risk scores had consistent C statistics across subgroups of age and treatment modality (Table 3). Predicted survival was also concordant with observed survival across risk groups and time points except for month 6 in the highest risk score group (ie, ≥ 95 th percentile of risk score) among patients with a last eGFR of 15 mL/min per 1.73 m² or higher (Figure 2). This group was the oldest population, and their overestimated survival may be explained by the early mortality phenomena among the elderly.

Our study results should be interpreted with several potential limitations in mind. First, the model performance may depend on the accuracy of data on comorbid conditions. We used specific ICD-9-CM codes in the CMS and administrative databases but were not able to confirm their accuracy. However, our prediction model was externally validated in the KPSC cohort where clinical practice is

different from that of the VA, suggesting little impact of this potential bias. Furthermore, by using diagnostic codes to identify the presence of comorbid conditions, our score lends itself to automated implementation in electronic medical records. Second, although prediction performances (C statistics) were similar for the development and internal validation for the VA cohort as well as the external KPSC cohort, overall calibration was better for the interval validation cohort (Supplemental Figure 2) as expected because of the survival differences in the KPSC and VA cohorts. Future model refinements may include a mixture of patient cohorts more representative of the general dialysis population. Third, timing to use this risk score would also affect the model performance because values in selected variables change over time. Although C statistics were consistent between veterans with different time periods between the last eGFR measurement and dialysis initiation (ie, < 6 vs ≥ 6 months) (Table 3), our model showed greater discrimination in the lower eGFR groups and the KPSC cohort, in whom the lag period was shorter than that of their counterparts. Fourth, our cohort consisted mostly of whites and blacks. Although the KPSC cohort included 11% Asians, predicted mortality should be interpreted with caution in races other than whites or blacks before being validated in a specific race. Lastly, we did not account for vascular access. However, several studies have found that the mortality risk associated with vascular access may largely be accounted for by patient characteristics.^{39,40}

CONCLUSION

A new prediction tool for mortality during the first year of dialysis was developed and externally validated among incident dialysis patients in the United States. This tool is available at our website www.DialysisScore.com, which allows clinicians, patients, and patient family members to obtain the predicted mortality at months 3, 6, 9, and 12 after dialysis initiation. Our new tool could help improve nephrology care and may facilitate shared decision making for individualized preparation for dialysis initiation in late stages of chronic kidney disease.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CMS** = Centers for Medicare and Medicaid Services; **eGFR** = estimated glomerular filtration rate; **ESRD** = end-stage renal disease; **ICD-9-CM** = *International Classification of Diseases*; **Ninth Revision** = *Clinical Modification*; **IQR** = interquartile range; **KPSC** = Kaiser Permanente Southern California; **PS** = prognostic score; **USRDS** = United States Renal Data System; **VA** = Veterans Affairs

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