ORIGINAL ARTICLE

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Validation of a model to predict six-month mortality in incident elderly dialysis patients

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ABSTRACT

Background and objectives: To evaluate RRT benefits and risks and to inform patients and their families about ESRD treatment options, we have developed a prognostic score to predict 6-month mortality in elderly ESRD patients initiating dialysis. Five independent predictors were identified and a point system was constructed: age 75 years or older (2 points), coronary artery disease (2 points), cerebrovascular disease with hemiplegia (2 points), time of nephrology care before dialysis [< 3.0 months (2 points); ≥ 3 to < 12 months (1 point)], serum albumin levels [3.0 - 3.49 g/dL (1 point); < 3.0 g/dL (2 points)]. Model performance was good in both discrimination and internal validation. Before adopting our risk score into practice, our aim is to externally validate this initial predictive model by assessing its performance on a new data set. **Methods:** We apply the predictive score developed in a cohort of CKD patients, aged 65 years and over who started dialysis between 2009 and 2016, to an independent cohort of ESRD patients, aged 65 years and over who started dialysis between 2017 and 2019, in our Nephrology department. The performance of the prediction equation created in development cohort, was assessed using discrimination and calibration metrics in the validation cohort. **Results**: Our validation study cohort included 168 individuals, with a mortality rate of 12.5% (n=21) within 6-months of dialysis initiation. Model performance in the validation cohort had an acceptable discrimination [AUC of 0.79; (95% confidence interval, 0.70 to 0.88)]. The Hosmer and Lemeshow goodness-of-fit test was not statistically significant, indicating good calibration of the model (χ^2, 5 degrees of freedom = 2.311; P = 0.805). **Conclusions**: Our predictive simple score based on readily available clinical and laboratory data demonstrates a good performance when externally validated, namely with respect to discrimination and calibration. Model validation is crucial for adequately informing patients and their families about ESRD treatment options and providing a more patient-centered overall approach to care. Before we start general implementation in clinical practice, our score needs further validation in larger patient cohorts.

Key Words: Prognosis Score; End-Stage Renal Disease; Elderly; Decision Making

INTRODUCTION

Mortality in chronic kidney disease (CKD) remains high, particularly among the elderly, who represent the most rapidly growing segment of the end-stage renal disease (ESRD) population in Western countries[1,2].

One of the challenges to clinicians caring for older CKD patients expected to progress to ESRD lies in the evaluation of the overall benefit of offering them renal replacement therapy (RRT). Thus, for evaluating RRT benefits and risks and informing patients and their families about ESRD treatment options based on a shared decision-making process, several scoring systems have been developed[3-7]. One of the concerns related to the available predictive scores is that those may be unsuitable for widespread application due to unproven generalizability.

Portugal has the one of the highest incidences and prevalence of ESRD in the world[8,9]. Considering the need to develop prognostic models adapted to the specificities of each population, we have recently developed a prognostic score for predicting early death in elderly ESRD patients initiating dialysis in a cohort of Portuguese patients[10].

This score had a good performance and it was internally validated using bootstrapping methods[11]. If possible, before adopting a risk score into practice, the prognostic score should be externally validated and tested in a group of patients different to the sample used to develop the score[11].

Therefore, the objective of this study is to validate the previously developed prognostic score in an independent dataset and compare its performance with other known scoring systems[4].

METHODS

A prospective cohort study was performed for external validation of our prognostic score[10]. The sample included all patients aged 65 years and over referred to the Nephrology Department of Centro Hospitalar Universitário do Porto (CHUP), who started dialysis as their first RRT between January 2017 and December 2019.

The study was performed in accordance with the Declaration of Helsinki and approved by CHUP's Institutional Review Board.

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Data was collected primarily from electronic clinical records and through information from dialysis centers. Demographic, clinical and functional variables were recorded. Glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology (CKD-EPI) 2009 creatinine equation[12]; all serum creatinine measurements were performed in the same laboratory using a calibrator for automated systems (*Roche Diagnostics*). Etiological diagnosis of CKD was based on the patient's history, kidney ultrasound, and kidney biopsy, when available.

Cognitive status was evaluated using the Mini Mental State Examination (MMSE)[13] with cognitive impairment defined for scores lesser or equal to 23. Functional dependency was defined as requiring assistance for transfer, classified as totally dependent or need assistance for transfer; otherwise, patients were classified as autonomous.

A modified version of the Charlson comorbidity index (mCCI)[14], i.e., by excluding subject's age and presence of kidney disease, was calculate and subdivided into three subgroups (0-2, 3-4, ≥5).

The outcome of interest was all-cause mortality within first 6 months of dialysis therapy initiation. In the validation cohort, vital status was checked until 30 December 2019.

The prognostic score that we intend to validate was developed in patients from the same center who started dialysis between January 2009 and December 2016. The design and detailed methodology used in the development of the prognostic model has been described previously[10].

■ Statistical Analysis

Data are reported as medians and interquartile range (IQR) or frequencies and proportions whenever appropriate.

Comparisons between groups for categorical data were made using the chi-square test. Continuous data were compared using the Mann-Whitney test for non-normally distributed variables.

The discriminative power of the prognostic score (i.e., the ability to identify patients at highest risk of dying within the first 6 months of starting dialysis) was assessed by calculating the area under the receiver operating characteristic (ROC) curves (AUC). Calibration of the risk score reflecting the link between predicted and observed risk was evaluated by the Hosmer-Lemeshow goodness-of-fit test (a P-value above 0.05 indicates acceptable calibration). The developed risk score in our work[10] and Couchoud score[4] was calculated for each patient to determine the performance of each scoring system in predicting mortality. The discrimination of each scoring system was assessed and compared using AUC.

A P value < 0.05 was considered statistically significant for all analyses. Data were analyzed using the STATA 13.0 and SPSS 26.0 (SPSS, Inc., Chicago, IL) statistical software.

■ Model Development

Briefly, our score[10] was developed using data from a cohort (development cohort) of 421 patients, aged 65 years and over who started dialysis between 2009 and 2016, in our Nephrology Service. Demographics and clinical variables were included as potential predictors. The predictive score was developed using a multivariable logistic regression analysis. A bootstrapping method[15,16] was used for internal validation.

Five independent predictors were identified and a point system was constructed: age 75 years or older (2 points), coronary artery disease (2 points), cerebrovascular disease with hemiplegia (2 points), time of nephrology care before dialysis [< 3.0 months (2 points); ≥ 3 to < 12 months (1 point)], serum albumin levels [3.0 - 3.49 g/dL (1 point); < 3.0 g/dL (2 points)] (Table I).

Table I

Predictors of 6-month mortality and associated risk scoring system

	Shrunken β-Regression Coefficient[a]	Risk score[b]
Age category (≥75 years vs. <75 years)	0.86	2
Coronary artery disease (yes vs. no)	0.83	2
Cerebrovascular disease with hemiplegia (yes vs. no)	0.84	2
Albumin category (ref: ≥ 3.5 g/dL)		
3.0 - 3.49 g/dL	0.76	1
< 3.0 g/dL	1.30	2
Time of nephrology care prior to dialysis (ref: ≥ 12 months)		
< 3.0 months	1.26	2
≥ 3 to < 12 months	0.56	1

[a] Original β-regression coefficient multiplied by heuristic shrinkage factor.

[b] Scores assigned by dividing the shrunken β-regression coefficients by 0.528 (two-fifths of the two small β-coefficients in the model) and rounded to nearest integer.

Model performance was good in both discrimination [AUC of 0.793; (95% confidence interval, 0.73 to 0.86)] and internal validation [concordance statistics of 0.791 (95% confidence interval, 0.73 to 0.85)].

With our model[10], we made a risk assessment questionnaire for clinicians' and patients' use, illustrated in Figure 1, exposing a simple understandable method for establishing a patient's risk for the outcome depending on an individual's status for the five variables included in the tool.

■ RESULTS

■ Baseline Characteristics of Study Participants

The validation cohort included 168 individuals aged 65 years or older. Baseline patient characteristics from the development and validation cohorts are summarized in Table II.

Compared to patients from the development cohort, patients from the validation set had lower eGFR at dialysis initiation and had fewer hospitalizations within 6-months prior to dialysis. Furthermore, patients included in the validation sample were more functionally autonomous and were referred earlier to nephrology care prior to dialysis.

Figure 1

Score chart to predict 6-months mortality

6-months mortality predictors	Assigned Points
Age (years) Points < 75 ..... 0 ≥ 75 2	
Coronary artery disease 2	
Cerebrovascular disease with hemiplegia 2	
Albumin (g/dL) ≥ 3.5 .....0 3.0 - 3.49 ..... 1 < 3.0 2	
Time of nephrology care (months) ≥ 12 .....0 ≥ 3 to < 12 ..... 1 < 3.0 2	

Total Score

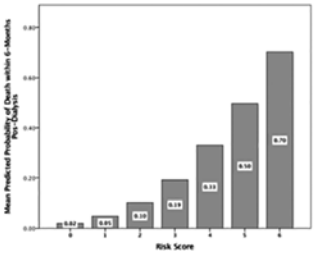


Figure 2

Performance of risk score in validation

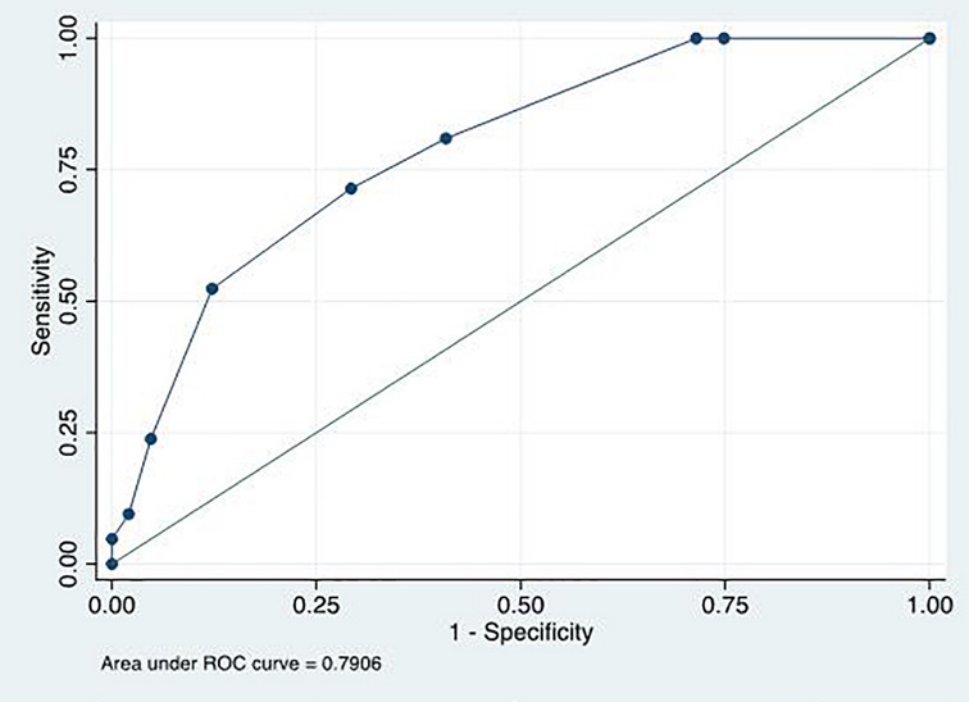


Table II

Baseline characteristics of development and validation cohorts for predicting 6-months mortality in elderly ESDR patients

	Development Cohort n=421	Validation Cohort n =168	*P* Value
Age (years), median and IQR	75.5 [70 – 80]	74.7 [69 – 80]	0.428
Age ≥75 years, n (%)	217 (51.5)	83 (49.4)	0.549
Female, n (%)	195 (46.3)	63 (37.5)	0.051
Primary renal disease, n (%)			
Diabetic nephropathy	156 (37.1)	59 (35.1)	
Ischemic nephropathy	69 (16.4)	28 (16.7)	
Glomerulonephritis	50 (11.9)	24 (14.3)	0.135
ADPKD	21 (5.0)	15 (8.9)	
Other	73 (17.3)	17 (10.1)	
Unknown etiology	52 (12.4)	25 (14.9)	
BMI (kg/m^2), median and IQR	25.7 [23.5 – 28.7]	26.1 [22.9 – 29.2]	0.840
< 25, n (%)	170 (40.4)	67 (40.6)	
25-30	148 (35.2)	63 (38.2)	0.791
> 30	75 (17.8)	35 (21.2)	
Cognitive impairment, n (%)	63 (15.0)	16 (9.5)	0.121
Totally dependent for transfer, n (%)	37 (8.8)	13 (7.7)	
Need assistance for transfer, n (%)	188 (44.7)	45 (26.8)	<0.001
Autonomous, n (%)	196 (46.6)	110 (65.5)	
Institutionalization, n (%)	22 (5.2)	8 (4.8)	0.817
mCCI, median and IQR	3.8 [2 – 5]	3.0 [2 – 5]	0.083
0-2, n (%)	127 (30.1)	59 (35.1)	
3-4	130 (30.9)	54 (32.1)	0.326
≥ 5	164 (39.0)	55 (32.7)	
Current/ Former smoking, n (%)	96 (22.8)	49 (29.1)	0.105
Diabetes, n (%)	212 (50.4)	88 (52.4)	0.657
Hypertension, n (%)	409 (97.1)	163 (97.0)	0.934
Dyslipidemia, n (%)	375 (89.1)	156 (92.9)	0.164
Congestive heart failure, n (%)	262 (62.2)	106 (63.0)	0.845
Coronary artery disease, n (%)	126 (29.9)	54 (32.1)	0.598
Cardiac arrhythmia, n (%)	101 (24.0)	41 (24.4)	0.915
Cerebrovascular disease, n (%)	137 (32.5)	40 (23.8)	0.116
with hemiplegia	43 (10.2)	14 (8.3)	0.486
Peripheral vascular disease, n (%)	165 (39.2)	55 (32.7)	0.144
Neoplasia, n (%)	64 (15.2)	31 (18.5)	0.333
COPD, n (%)	74 (17.6)	36 (21.4)	0.279
Chronic liver disease,, n (%)	30 (7.1)	8 (4.8)	0.292
Autoimmune disease, n (%)	16 (3.8)	11 (6.5)	0.150
Peptic ulcer, n (%)	62 (14.7)	27 (16.0)	0.681
Albumin <3.5 g/dL, median and IQR	3.6 [3.2 - 4.0]	3.7 [3.1 - 4.2]	0.198
≥ 3.5, n (%)	255 (60.6)	101 (60.1)	
3.0 - 3.49	87 (20.7)	36 (21.4)	0.978
< 3.0	79 (18.8)	31 (18.5)	
Creatinine (mg/dL), median and IQR	6.3 [4.7 - 7.5]	6.6 [5.1 – 8.2]	0.003*
eGFR EPI (ml/min/1.73 m^2), median and IQR	6.5 [4.8 – 8.4]	5.6 [4.3 – 7.7]	0.003*
≥ 15, n (%)	12 (2.9)	2 (1.2)	
10 – 14.9	43 (10.2)	7 (4.1)	
< 10	366 (86.9)	159 (94.6)	0.025*
Time of nephrology care before dialysis (months), median and IQR	43.9 [18.0 -89.0]	65.2 [27.4 -126.5]	<0.001*
< 3; n (%)	83 (19.7)	17 (10.1)	
≥3 to < 12	43 (10.2)	9 (11.3)	0.02*
≥12	295 (70.1)	142 (84.5)	
Dialysis modality: hemodialysis; n (%)	411 (97.6)	154 (91.7)	0.001*
Unplanned dialysis, n (%)	249 (59.1)	85 (50.6)	0.059
Access at first dialysis: catheter, n (%)	181 (42.9)	68 (40.5)	0.577
Hospitalizations 6-months before dialysis, n (%)	144 (34.2)	75 (44.6)	0.018*

Data expressed as medians and interquartile ranges (IQR) or n (%) when appropriate. Comparisons between continuous variables were done using a nonparametric test (Mann-Whitney test); associations between categorical variables were analyzed using the χ^2 test; *P<0.05. BMI, body mass index; mCCI, modified Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; eGFR, estimated Glomerular Filtration Rate using the Chronic Kidney Disease Epidemiology; Nº hospitalizations, number of hospitalizations based on 6 months prior to dialysis initiation. *P<0.05

Independent Validation

Among patients in the validation cohort, there were 21 deaths (12.5%) within the first 6 months of dialysis initiation.

In the validation set (n=168), the performance of the prognostic score is shown in Figure 2, with an AUC of 0.79 (95% CI 0.70-0.88) indicating acceptable (nearly good) discrimination. The Hosmer and Lemeshow goodness-of-fit test was not statistically significant, indicating good calibration of the model (χ^2, 5 degrees of freedom = 2.311; P = 0.805).

Comparison with Alternative Risk Score

Couchoud score[4] was calculated for all patients in the validation cohort according to corresponding formula, with an AUC of 0.766 (95% CI 0.65–0.88). In this cohort, the performance of our score was higher than Couchoud score, but not statistically significant (P = 0.63) (Figure 3).

DISCUSSION

Incorporating predictive models into CKD management for older patients may help to inform patients and their families about ESRD treatment options and provide a more patient-centered overall approach to care.

Risk prediction models are based on equations designed on the basis of prognostic factors and clinical outcomes, available at the time the prediction is made, and collected in specific and representative cohorts of individuals followed up for a given period of time[17,18].

The performance of a risk prediction model is commonly assessed by testing its calibration and discrimination. Calibration describes the agreement of observed and predicted event rates[19]. Discrimination expresses the ability of the prediction model to distinguish individuals who will develop the outcome of interest from those who will not[20].

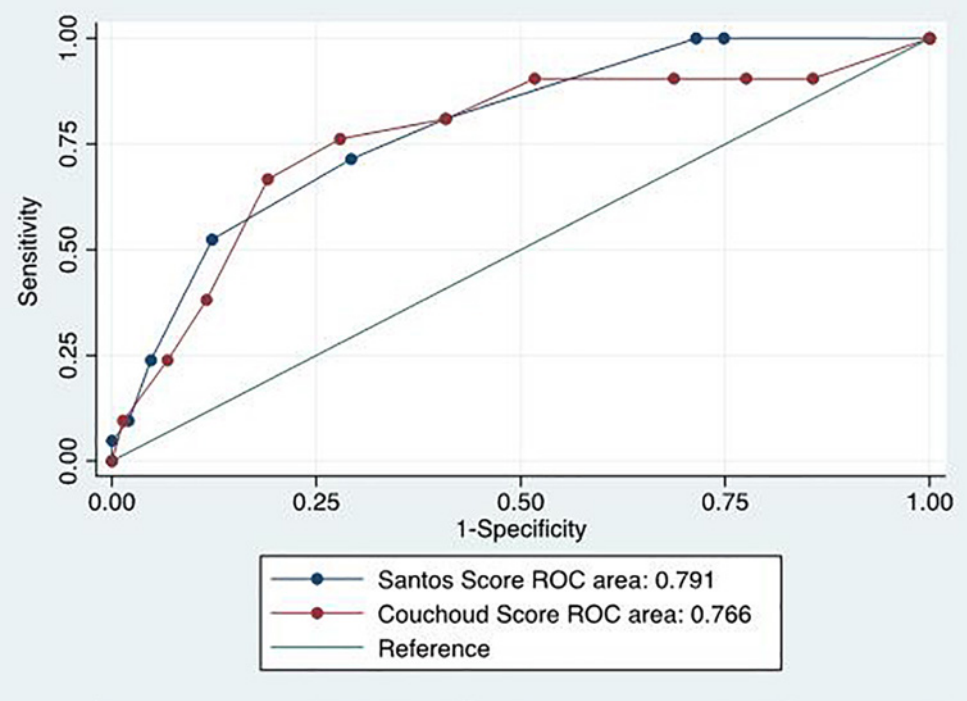
Another important question for physicians to consider is whether the score accurately predicts outcomes in people like their patients. So, validation of prognostic models is a determinant step before we start implementation in clinical practice. Models should be internally and especially externally validated to obtain reliable estimates of model performance[11].

Internal validation implies assessment of model performance directly in the derivation cohort. This approach yields an optimistic estimate of model performance[17,18]. To minimize this limitation, the model can be developed on the whole dataset and data reuse methods, such as cross-validation and bootstrapping, applied to assess performance[11,17,18].

In the derivation of our score[10] we performed a bootstrapping procedure (5000 bootstrap samples) to internally validate the risk

Figure 3

Comparison with Couchoud Score



score, which generated a concordance statistics of 0.791 (95% confidence interval, 0.73 to 0.85) and an optimism of 0.002.

Even with a good performance achieved in the same cohort as the one that was used to develop the model, before adopting a risk score into practice, clinicians need to decide whether the score accurately predicts outcomes in a sample similar to their patients but belonging to a different source population; therefore, validation in an independent sample is required[11].

In the past years, several mortality scores have been developed on the basis of various combinations of comorbidities and laboratory data, but only a few of them have focused on short-term survival including only elderly CKD patients[3-7]. Also, only a few of the models were externally validated [21-23].

Portugal has one of the highest unadjusted incidences of ESRD among European countries[8]. About 64% of the incident dialysis patients in 2018 were over 65 years with a mean age of 67.2 years for prevalent patients[24], above the mean age of the European registry[8].

Differences in patients' profiles, namely distinct sociodemographic and clinical characteristics between the cohorts used to derive those scores, reinforce the need to develop predictive scores adapted to the specificities of each population. With this in mind, we have recently developed a prognostic score for predicting early death in elderly ESRD patients initiating dialysis that has been derived and internally validated in a cohort of Portuguese patients[10].

This score is based on simple and readily available information. With respect to model performance, the proximity of the AUC generated by bootstrapping procedure to the observed AUC and a very acceptable optimism indicate a good discrimination ability of our score. The good performance (its calibration and discrimination) of our model on the new data (validation group), indicated that the model was likely not overfit, and demonstrated its predictive accuracy.

In the development cohort, the performance of our risk score was significantly higher than Couchoud score[4], which reflects the different characteristics of the populations involved in derivation of the models. Also, in the validation cohort, although not statistically significant, the performance of our score was higher than Couchoud score[4].

Bansal et al.[21] developed a prediction equation for 5-year risk of mortality for older people with CKD stages 3-5 not treated with dialysis. The equation included nine readily available clinical variables (age, sex, race, eGFR, urine albumin-to-creatinine ratio, smoking, diabetes mellitus, and history of heart failure and stroke), and it was externally validated in a large cohort of elderly CKD patients. This model has an acceptable calibration and discrimination in both the development (C-statistic = 0.72; 95% confidence interval, 0.68 to 0.74) and validation cohort (C-statistic = 0.69; 95% confidence interval, 0.64 to 0.74). However, one of its limitations is that the validation cohort did not fit the frailty phenotype associated with CKD[26] because the authors enrolled well-functioning men and women, and it has been well established that frailty is an additional risk factor for mortality in CKD patients [21].

It is important to highlight any differences that might affect model translation between the validation sample and the original study sample. The differences in the baseline characteristics between our validation and development population are shown in Table II. Patients from the validation set had lower eGFR at dialysis initiation, had fewer hospitalizations within 6-months prior to dialysis, were more functionally autonomous and were referred earlier to nephrology care than patients from the development cohort. These differences may be due to the difference in timing of dialysis initiation, as the validation cohort was more recent than the development cohort.

Even so, our model achieved a good performance in the validation cohort, which confirms its predictive accuracy in a different source population, i.e.; it is independently validated.

Floege et al.[23] have published another risk prediction model developed in a European hemodialysis cohort with a mean age of 64 years old, using objective measurements. This model was then validated in an external cohort of the Dialysis Outcomes and Practices Patterns Study (DOPPS) and exhibited a moderate discrimination (C-statistic of 0.68 to 0.79). Nevertheless, contrary to our model[10], the Floege et al. score[23] has not been developed nor validated in a cohort of elderly dialysis patients. In addition, because the development cohort includes only patients who survived the first 3 months, whereas the validation cohort of DOPPS includes mainly prevalent patients, it is still not a perfect risk predictor for frail elderly, in which the risk of short-term mortality is what needs to be predicted.

The Couchoud et al. model[4] was externally validated in a US population[22]; although investigators modified the score; poor performance was observed with respect to prediction of 6-month mortality in older patients with ESRD commencing dialysis. Although the sample size of our validation cohort has a limited pool of subjects compared to the development cohort, inherent to a single-center validation study, the validation sample included data on all the variables in the derivation model[10].

Simplicity of models and reliability of measurements are important criteria in developing clinically useful prognostic models[11]. Our predictive score[10] includes variables that are well defined, measurable, and readily available; in other words; our model is clinically useful.

There are some limitations in our study. First, this is a single-center study, with a relatively small sample size. Secondly, our population consisted of incident dialysis patients that were referred to nephrologists. Those who were not referred, not selected for, or not accepted for dialysis initiation, were not included. Our model may, therefore, not be generalizable to the entire population of elderly ESRD patients.

In conclusion, after development, our score was independently validated in a new dataset of patients indicating acceptable discrimination to predict early mortality for elderly CKD patients who initiate dialysis. This simple and accurate prediction score based on readily available data can be an easily implemented tool to apply in daily practice to guide patient care.

■ Ethical Statement

The study was performed in accordance with the Declaration of Helsinki and approved by the CHUP Institutional Review Board. The subjects have given their informed consent.

■ Author Contributions

The authors contributed to this article in the following way: Study design: JS, IF; data collect: JS, AC, SO; data analysis: JS, PO, IF; methodology: JS, PO, AC, LL, IF; manuscript preparation: JS, IF.

Disclosure of potential conflicts of interest: none declared

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