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Original Paper

Derivation and Validation of Risk Scores to Predict Cerebrovascular Mortality Among Incident Peritoneal Dialysis Patients

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Key Words
Cerebrovascular diseases • Mortality • Peritoneal dialysis • Risk prediction

Abstract
Background/Aims: Cerebrovascular disease (CeVD) is one of the leading causes of death in patients initialising peritoneal dialysis (PD). Currently there is no risk score to predict the future risk of CeVD on entry into PD. This study aimed to derive and validate a risk prediction model for CeVD mortality in 2 years after the initialisation of PD. ***Methods:*** All patients registered with the Henan Peritoneal Dialysis Registry (HPDR) between 2007 and 2014 were included. Multivariable logistic regression modelling was applied to derive the risk score. All accessible clinical measurements were screened as potential predictors. Internal validation through bootstrapping was applied to test the model performance. ***Results:*** The absolute risk of CeVD mortality was 2.9%. Systolic and diastolic blood pressure, total cholesterol, phosphate, and sodium concentrations were the strongest predictors of CeVD mortality in the final risk score. Good model discrimination with C statistics above 0.70 and calibration of agreed observed and predicted risks were identified in the model. ***Conclusion:*** The new risk score, developed and validated using clinical measurements that are accessible on entry into PD, could be used clinically to screen for patients at high risk of CeVD mortality. Such patients might benefit from therapies reducing the incidence of CeVD related events.

Introduction

Cardiovascular disease is the leading cause of death in patients with kidney failure treated by dialysis [1, 2]. Although much focus has been on their high rates of myocardial infarction, cardiomyopathy, and cardiac arrhythmia, less attention has been given to

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the equally debilitating burden of cerebrovascular disease [3, 4]. The high incidence of haemorrhagic and ischemic stroke in individuals receiving hemodialysis (HD) and in those undergoing peritoneal dialysis (PD) is a significant concern [5]. In leveraging a country-wide comprehensive medical records system in Taiwan, Wang et al. [6] reported a 2- to 6-fold higher risk of stroke in HD and PD patients compared with age- and sex-matched individuals from a non-dialysis reference group from the general population. When adjusted for baseline comorbid conditions, HD and PD patients had comparable but much higher hazards for ischemic (2.88 and 3.21, respectively) and haemorrhagic stroke.

In clinical practice, identification of individuals at high risk of cerebrovascular disease can assist the tailoring of more intensive, personalised management to improve patient prognosis. For this specific reason, several risk scores have been derived for the prediction of cerebrovascular disease in general population [7, 8] and other specific populations, such as those with diabetes [9]. However, there have been no risk scores developed for incident peritoneal dialysis patients to predict their risk of cerebrovascular mortality.

Furthermore, unlike the situation in health care systems in many developed countries, a complete medical history is unlikely to be obtained under the health care systems in most developing countries due to limitations in the primary and secondary care systems inaccurately recording pre-existing comorbidities [10, 11]. There could be information bias in this setting if the risk algorithm developed depended upon the medical history that was self-reported by the patient. There is therefore a need for a risk prediction model that could predict future cerebrovascular death, mainly utilising objective clinical measurements likely to be accessible in most developing countries.

The aim of this study was to derive and validate a risk algorithm to predict the 2-year risk of cerebrovascular mortality among incident peritoneal dialysis patients.

Materials and Methods

Data setting and study population

In this study, data from the Henan Peritoneal Dialysis Registry (HPDR) were used to derive and validate the risk prediction model. Situated in Central China, Henan is a province with over 100 million population. Briefly, the HPDR is administrated under the auspices of the Department of Nephrology, the First Affiliated Hospital of Zhengzhou University which is in charge of an independent audit and analysis of medical care for renal disease in the province [12]. Over the study period, patients' information was prospectively collected electronically from all nephrological departments across the province. All data ma at the HPDR are subjected to an algorithm which identifies suspicious measurements, which are then further examined and corrected where necessary by contacting the nephrological department. This study was designed as a cohort study, which included all patients aged >= 18 years (n=3,070) who commenced PD between 2007-2014 and who had at least 2 years' follow-up after baseline measurement. Patients who died (n=5), underwent kidney transplant (n=9) or whose renal function recovered (n=2) within 90 days after initialisation of dialysis were excluded to avoid a reverse causality association between candidate predictors and primary outcome (final n=3,054). This reflects the standard approach to investigating "real" ESRD patients among all those initialising PD care.

Ethics approval was granted by the Clinical Research Ethics Committee of the First Affiliated Hospital of Zhengzhou University. Written informed consent was obtained from all participants before inclusion.

Defining outcome, predictors, missing data and power calculation

The primary outcome in the study was defined as recorded death with clinical diagnosis of cerebrovascular disease [13, 14].

All available patients' information, covering self-reported comorbidities, demographic characteristics, and clinical measurements (262 variables) were collected by the time of initialising the PD for review by 5 clinicians. Variables agreed to be clinically relevant by ≥3 clinicians were included in the analysis for further evaluation as candidate predictors. Backward elimination within a multivariable logistic regression model,

with all candidate predictors, was applied to pin down the parameters for the final prediction model. For predictors included in the final model, our cohort had missing information on body mass index (13.51%), phosphate (20.92%), albumin (19.92%), total protein (22.57%), total cholesterol (24.25%), low density lipoprotein (24.58%), fasting glucose (15.92%), sodium (8.02%), systolic blood pressure (4.82%), and diastolic blood pressure (4.82%). Multiple imputation was applied to replace missing values by using a chained equation method based on all candidate predictors and primary outcome to improve the model accuracy [15, 16, 17]. 30 imputed datasets were generated for missing predictors that were then combined across all datasets by using Rubin's rule to generate final model estimates [18]. With 89 cerebrovascular deaths during the first 2 years of initialising PD and 11 predictors in the final derivation cohort, an effective sample size was estimated with 8 final events per predictor, close to the minimum requirement suggested by Peduzzi et al. [19].

Model development and validation

In this study, cerebrovascular mortality within the first 2 years of initialising PD was tackled as a binary outcome measure. A univariable logistic regression model was used to estimate the unadjusted odds ratio for each candidate parameter. Candidate predictors that were not statistically significant were excluded from the multivariable Logistic regression model by backward elimination ($P > 0.1$ based on change in log likelihood) [20]. Excluded predictors were reinserted into the final prediction model to further examine whether they turned statistically significant, however, none were significant. Two-degree fractional polynomial terms were used to model non-linear associations between outcomes and continuous predictors [21]. Fractional polynomial parameters were also re-checked at this stage and re-estimated when necessary. The risk score is calculated as the log odds from the final prediction model with the selected predictors (and polynomials), and the predicted risk is derived from the log odds [18].

Model calibration was assessed by plotting the mean predicted probability against the mean observed proportion of cerebrovascular mortality by tenth of predicted risk. Model discrimination was assessed with the concordance statistic (C-statistic). A value of 0.50 represents no discrimination and 1.00 represents perfect discrimination. Internal validation of the model discrimination was assessed by calculating the bootstrap optimism-corrected c-statistic with 100 bootstrap replications.

To facilitate model utilisation in clinical practice, the logistic regression equations were transformed into prognostic score charts. The coefficients in the logistic regression equation were multiplied by 50 and rounded to the nearest integer to obtain the prognostic score per predictor. Multiplication by 50 was chosen to ensure that a majority of the coefficients were close to being an integer, thereby minimizing the effects of rounding. The sum of all prognostic scores reflects patients' probability of cerebrovascular mortality.

We used Stata V15.1 for all statistical analyses. This study was conducted and reported in line with the Transparent Reporting of a multivariate prediction model for Individual Prediction Diagnosis (TRIPOD) guidelines [22].

Results

Study participants

In our cohort, we analysed information on 3,054 patients with 89 cerebrovascular deaths within 2 years of initialisation of PD. The population characteristics measured at baseline for the study population are presented in Table 1.

Model development and model performance

Among the 26 candidate predictors, 18 parameters from 11 predictors through backward elimination remained in the final model (Table 2). With optimism adjustment, the final prediction model was able to discriminate patients initialising PD with and without cerebrovascular mortality with a C statistic of 0.744 (95% confidence interval 0.699 to 0.788). Good apparent calibration was presented as the agreement between the observed and predicted proportion of events (Fig. 1). Table 3 and Fig. 2 illustrate the risk prediction equations with real clinical examples.

Table 1. Baseline Characteristics of study cohort. Binary variables are displayed as numbers (percentage) and continuous variables are displayed as median (interquartile)

Candidate Predictors	Derivation Cohort
N	3,054
Cerebrovascular Deaths, n (%)	89 (2.9)
Male Gender, n (%)	1,790 (58.6)
Primary Glomerular Disease, n (%)	1,446 (47.3)
Age, years	48.9 (38.0 to 59.0)
Haemoglobin, g/L	88.0 (75.0 to 102.0)
Packed cell volume	19.0 (2.3 to 27.5)
Reticulocyte, %	34.9 (13.1 to 60.2)
Phosphate, mg/dl	1.8 (1.4 to 2.2)
Albumin, g/L	33.6 (29.7 to 37.8)
Total iron binding capacity, µmol/L	45.0 (35.0 to 52.6)
FeTIBC, mmol/L	25.0 (20.9 to 41.1)
Creatinine, µmol/L	837.0 (633.0 to 1066.0)
estimated Glomerular Filtration rate, mL/min/1.73 m^2	4.8 (3.6 to 6.9)
Transferrin, mg/dl	194.9 (119.9 to 399.4)
Total protein, g/L	57.6 (52.0 to 63.0)
Prealbumin, mg/L	294.0 (197.4 to 363.0)
Total Cholesterol, mmol/L	4.4 (3.6 to 5.2)
Low density lipoprotein, mmol/L	2.6 (1.8 to 3.4)
Fasting glucose, mmol/L	4.9 (4.3 to 5.9)
Sodium, mEq/L	140.0 (136.9 to 142.3)
C-reaction protein, mg/dl	2.4 (1.0 to 5.3)
Body mass index, kg/m^2	22.7 (20.7 to 24.9)
Systolic blood pressure, mmHg	145.0 (135.0 to 159.0)
Diastolic blood pressure, mmHg	86.0 (80.0 to 95.0)
Cerebrovascular diseases, n (%)	1,384 (45.3)
Type 2 Diabetes, n (%)	449 (14.7)
Taking antihypertensive treatment, n (%)	1257 (41.2)

Table 2. Final multivariate analysis for cerebrovascular mortality risk within two years of initialisation of peritoneal dialysis

Predictors	Coefficient	95% Confidence Interval
(BMI/10)^3	0.626533	(-0.030687 to 1.283753)
Ln(BMI/10)*(BMI/10)^3	-0.475435	(-1.001754 to 0.050883)
[(phosphate+0.9491628725516048)/10]^3	3.143257	(-22.169120 to 28.455630)
[(phosphate+0.9491628725516048)/10]^3*Ln[(phosphate+0.9491628725516048)/10]	0.148686	(-41.275240 to 41.572610)
[(total protein)/100]^-2	-0.032448	(-1.046089 to 0.981193)
[(total protein)/100]^-2*Ln[(total protein)/100]	0.044152	(-0.687377 t0 0.775681)
[(total cholesterol+1.673428429186277)/10]^0.5	-4.935679	(-20.685340 to 10.813990)
[(total cholesterol+1.673428429186277)/10]^0.5*Ln[(total cholesterol+1.673428429186277)/10]	3.353445	(-7.293830 to 14.000720)
(sodium/100)^3	8.310844	(-6.262589 to 22.884280)
(sodium/100)^3*Ln(sodium/100)	-14.405770	(-37.254140 to 8.442614)
(systolic blood pressure/100)^-2	-3.144864	(-6.204293 to -0.085436)
(systolic blood pressure/100)^-2*Ln(systolic blood pressure/100)	-8.223230	(-14.442550 to -2.003909)
(diastolic blood pressure/100)^3	0.651553	(-1.649131 to 2.952236)
(diastolic blood pressure/100)^3*ln(diastolic blood pressure/100)	-3.360246	(-10.423590 to 3.703100)
Age	0.007272	(-0.013218 to 0.027763)
Albumin	-0.058305	(-0.103438 to -0.013172)
Low density lipoprotein cholesterol	-0.104797	(-0.317004 to 0.107411)
Glucose	0.024396	(-0.056247 to 0.105039)
Constant	-6.785156	(-31.849070 to 18.278760)

Fig. 1. Calibration of the prediction model—the observed 2-year probability of Cerebrovascular mortality by tenths of model-predicted probability.

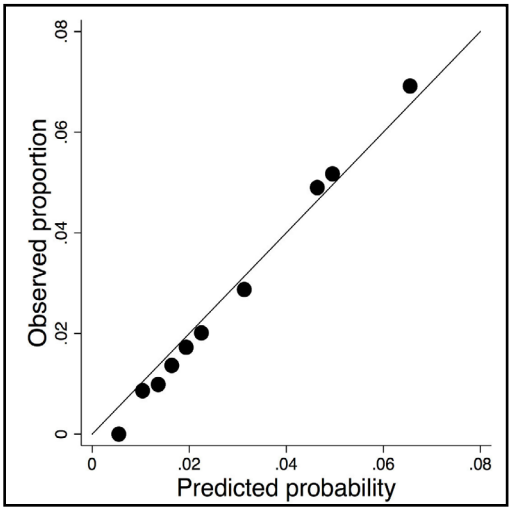

Table 3. Prognostic score chart for predicting cerebrovascular mortality among incident peritoneal dialysis patients. Clinical example: 52 years old, 21.87 kg/m2 of body mass index, 1.53 mg/dl phosphate, 2.45g/L total protein, 2.45mmol/L total cholesterol, 124 mEq/L sodium, 136 mmHg systolic blood pressure, 84 mmHg diastolic blood pressure, 3.05mmol/L low-density lipoprotein cholesterol and 7.1 mmol/L glucoseFP term, indicates fractional polynomial term

Predictors	Description	Value	Score
Body mass index-FP term 1	(BMI/10)^3	13.623	680
Body mass index-FP term 2	Ln(BMI/10)*(BMI/10)^3	-10.590	-529
Phosphate-FP term 1	[(phosphate+0.9491628725516048)/10]^3	0.048	2
Phosphate- FP term 2	[(phosphate+0.9491628725516048)/10]^3*Ln[(phosphate	-0.003	0
Total protein- FP term 1	[(total protein)/100]^-2	-0.084	-4
Total protein FP term 2	[(total protein)/100]^-2*Ln[(total protein)/100]	-0.054	-3
Total cholesterol- FP term 1	[(total cholesterol+1.673428429186277)/10]^0.5	-3.169	-158
Total cholesterol- FP term 2	[(total cholesterol+1.673428429186277)/10]^0.5*Ln[(total cholesterol+1.673428429186277)/10]	-1.908	-95
Sodium- FP term 1	(sodium/100)^3	15.846	792
Sodium FP term 2	(sodium/100)^3*Ln(sodium/100)	-5.908	-295
Systolic blood pressure-FP term 1	(systolic blood pressure/100)^-2	-1.700	-85
Systolic blood pressure- FP term 2	(systolic blood pressure/100)^-2*Ln(systolic blood pressure/100)	-1.367	-68
Diastolic blood pressure- FP term 1	(diastolic blood pressure/100)^3	0.386	19
Diastolic blood pressure- FP term 2	(diastolic blood pressure/100)^3*ln(diastolic blood pressure/100)	0.347	17
Age	(BMI/10)^3	0.378	19
Albumin	Constant=1	-1.166	-58
Low density lipoprotein cholesterol		-0.320	-16
Glucose		0.173	9
Constant		-6.785	-339
Sum Score		-114	
Predicted probability of cerebrovascular hospitalisation		9.3%	

Discussion

We have developed and validated a new risk prediction model to estimate the individual level absolute risk of cerebrovascular mortality during the first 2 years of initialisation of PD in a representative Chinese sample of patients. Both good model calibration and discrimination, with a C statistic of greater than 0.70 were found in the final risk prediction model.

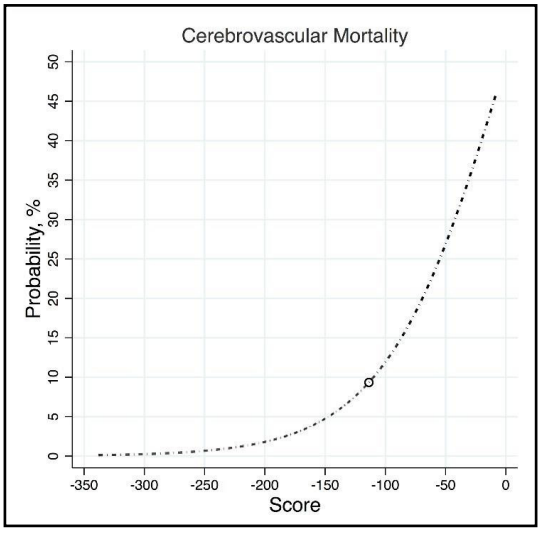

Fig. 2. Graphical illustration of cerebrovascular mortality prognostic score for the clinical example.

This newly developed risk prediction model has several advantages for its application in most developing countries. This risk prediction model is based on individual level absolute risk developed and validated in a prospective cohort. It is derived from reliable clinical measurements that are usually performed among patients initialising PD, implying that it can be readily applied in routine clinical practice. The model is amenable to further external validation in many regions and countries that operate routine PD care.

The methods used to derive and validate the model are close to those for other risk prediction models developed from the CPRD and QResearch databases [21, 23]. The data used in this study were the largest dataset used for risk algorithms among patients initialising PD care. As the only PD registry data, HPRD includes all patients initialising PD care in Henan who are followed up for their lifetime; therefore, responder bias and selection bias were minimised in this study. Being located in Henan, the province with the second largest population in China, the population used in this study is likely to be a nationally representative sample.

Our study had some limitations. First, patients in this study were distinctively different from European ESRD patients in some characteristics, e.g. younger age, lower prevalence

of comorbidities, lower percentage receiving treatment and lower BMI. This suggests that more adjustments in these confounders might be needed when applying this risk prediction model into external ESRD populations, especially European patients with ESRD [4]. Second, some conventional cardiovascular risk factors, such as lifestyle risk factors (i.e. smoking) and previous health status information were not accessible in this study. Third, the relatively high volume of missing values in some variables, e.g. albumin and phosphate might potentially have impacted upon the extrapolation of the risk algorithm especially in the external population, this impact should have been reduced through the development of the risk prediction model using imputed datasets. Fourth, although patients in some developing regions/countries where access to, or the validity of, prior health records on cerebrovascular risk factors and multi-comorbidity are restricted might benefit from this risk prediction tool, further external validation in other distinctively different cohorts would still be warranted. Fifth, the distinctive threshold of absolute risk to define "high-risk" ESRD patients was not suggested in our study, as this definition would need to balance cerebrovascular mortality risks and clinical benefits for patients and analyse cost effectiveness, which exceeded this study scope. Finally, as cause of death can sometimes be uncertain, leading to outcome misclassification, future external validation studies are further warranted in other populations.

All potential clinical measurements in HPDR were reviewed by a review panel with 5 independent clinicians and considered as candidate predictors following a consensus process (agreed by ≥3 clinicians). This prediction model is different from currently existing risk algorithms derived in developed countries, through the exclusion of comorbidities, inconsideration of the difficulties in accessing and validating such data that are not routinely recorded in the under-developed primary care system in China.

The majority of predictors included in the risk algorithm are reliable and accurate clinical measurements [10] that are routinely collected at the time of entry into PD and accessible across Chinese PD clinical centres [24]. Moreover, the risk of recall bias in this study was potentially low with the limited use of self-reported information. Based on these, this risk prediction model can be readily validated within other external cohort or registry datasets.

Conclusion

Our study has developed a tool that predicts the 2-year risk of cerebrovascular mortality among incident peritoneal dialysis patients. Our prediction model has two important implications for clinical practice. First it can be used to screen populations at high risk for cerebrovascular mortality on initiating PD. The algorithm is based on readily accessible clinical data recorded in the PD registration database which can be reviewed by the PD/ESRD management team. It can be readily integrated into a PD registration computer system or an application for a handheld device for easy use. Secondly, this prediction tool could be used to establish treatment thresholds in PD clinical care through consensus development of national guidance.

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Disclosure Statement

The authors declare that they have no competing interests.

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