



Development of long-term cardiovascular disease risk prediction model for hemodialysis patients with end-stage renal disease based on nomogram

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Background: Chronic kidney disease (CKD) is a leading public health problem worldwide. Cardiovascular diseases are the primary cause of death in hemodialysis patients with CKD. Therefore, it is necessary to develop a simple risk assessment tool for cardiovascular events in hemodialysis patients with CKD.

Methods: A cohort of 370 hemodialysis patients, who were recruited between January 2015 to September 2019 in south China, were involved in the present study. On the basis of routine blood test indicators and ultrasonic cardiogram parameters, the optimal parameter set was determined and a Cox proportional hazards model coupled with a nomogram was used to predict cardiovascular risk over 3, 5, and 10 years. Predictive performance was evaluated using Harrell's concordance index (C-index) and the area under the receiver-operating characteristic curve (AUROC). The results were validated using both 10-fold cross-validation and hold-out validation (70% training and 30% validation, repeated 100 times).

Results: The optimal parameter set consisted of hypertension, diabetes mellitus, age, phosphate, triglyceride, C-reactive protein, white blood cells, and interventricular septum thickness. The time-dependent AUROCs for predicting 3-, 5-, and 10-year cardiovascular event occurrence risk were 0.836, 0.845, and 0.869, respectively. The nomogram showed satisfactory prediction performance (C-index: 0.808, 95% confidence interval: 0.773–0.844) and was well-calibrated. The results were further confirmed by 10-fold cross-validation and hold-out validation (C-index: 0.794 and 0.798, respectively).

Conclusions: On the basis of several easy-to-detect clinical parameters, we developed a simple and useful nomogram for predicting cardiovascular risk in long-term hemodialysis patients that is of potential value for clinical application.

Keywords: Nomogram; chronic kidney disease (CKD); cardiovascular event; hemodialysis; prediction

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Introduction

Chronic kidney disease (CKD) has been recognized as a leading public health problem worldwide, with high morbidity and mortality (1-3). Kidney failure, especially end-stage kidney disease (ESKD), is a leading cause of mortality. Patients with ESKD require kidney replacement therapy, including hemodialysis, abdominal dialysis, and renal transplant. In hemodialysis patients, cardiovascular events are the primary cause of death, and more than half of known deaths are related to cardiovascular causes (4). Therefore, risk assessment of cardiovascular events and individualized management and treatment for hemodialysis patients are necessary. The development of a simple and visual clinical assessment tool has the potential to achieve these goals.

The most commonly used model to predict the rate of cardiovascular events is the Framingham risk score (FRS) (5). The FRS was developed to predict the cardiovascular risk for the general population in 10 years by considering traditional risk factors, including cigarette smoking, elevated blood pressure, elevated serum total cholesterol (TC), low serum high-density lipoprotein (HDL) cholesterol, diabetes mellitus (DM), and advanced age. However, several researchers have noted that some risk factors predicting high cardiovascular mortality (CVM) in hemodialysis patients may differ from those in the general population (6,7). Therefore, using the FRS to assess cardiovascular risk in hemodialysis patients may be inadequate, for some factors, such as low blood pressure and low TC (rather than high blood pressure and high TC), are associated with higher cardiovascular mortality and total mortality in ESKD in the reverse epidemiology (8,9). Anker *et al.* developed 2 separate risk scores, CVM and CVM and mortality (CVMM), for hemodialysis patients (10). Both risk scores were found to be more predictive than FRS, and additionally, the CVM score was more predictive than the CVMM score. We speculated that patients with non-fatal and fatal cardiovascular events might have diverse risk factors. Therefore, it is important to use different evaluation indicators to evaluate the risk of non-fatal or fatal cardiovascular events.

In the present study, we used the time of the first cardiovascular event, routine blood test indicators, and ultrasonic cardiogram (UCG) parameters to build a Cox proportional hazards model and to further to construct a nomogram to predict the risk of cardiovascular event occurrence in 3, 5, and 10 years among long-term hemodialysis patients. Our nomogram-based risk prediction

model is a simple and visual assessment tool, and may be valuable to identify high-risk patients for earlier intervention.

We present the following article in accordance with the TRIPOD reporting checklist (available at <http://dx.doi.org/10.21037/apm-21-286>).

Methods

Study population and ethics

A cohort of 370 patients with hemodialysis were enrolled in the present study. The patients were recruited between January 2015 and September 2019 at the hemodialysis centers of the Third Affiliated Hospital of Southern Medical University and the Third Affiliated Hospital of Sun Yat-sen University. Inclusion criteria were hemodialysis >3 months due to renal failure. Exclusion criteria included non-renal failure, dialysis duration <3 months, and irregular dialysis. The end time of follow-up was May 31, 2020. The study was approved by the institutional review board of the Third Affiliated Hospital of Southern Medical University and the Third Affiliated Hospital of Sun Yat-sen University. All participants provided informed written consent before participating in the study. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Serum sample collection and test

Overnight fasting (12 h) blood samples were collected from all patients before first hemodialysis between January 2015 and September 2019. Biochemical measurements of procalcitonin, intact parathyroid hormone, serum ferritin (FER), serum phosphate, TC, triglyceride (TG), HDL, low-density lipoprotein cholesterol (LDL), apolipoprotein A, apolipoprotein B, C-reactive protein (CRP), white blood cells (WBC), hemoglobin (HB), platelet count, neutrophil absolute value (NEUT), lymphocyte absolute value, creatinine (CRE), blood urea nitrogen, serum calcium, uric acid, blood glucose (GLU), unsaturated iron-binding capacity, total iron-binding capacity, creatine kinase MB (CK-MB), and estimated glomerular filtration rate were performed using standard laboratory procedures.

UCG

UCG was performed by trained operators before first

hemodialysis at the radiology centers in the Third Affiliated Hospital of Southern Medical University and the Third Affiliated Hospital of Sun Yat-sen University between January 2015 and September 2019. The test included aortic root diameter, left atrium diameter (LAD), right ventricle diameter (RVD), left ventricular end-diastolic diameter, main pulmonary artery diameter, interventricular septum thickness (IVST), left ventricular posterior wall thickness (LVPWT), ejection fraction (EF), left ventricular fraction shortening, mitral valve peak E velocity (E), mitral valve peak A velocity (A), and the ratio of E/A.

Outcome

We defined the development of the first non-fatal and fatal cardiovascular event after hemodialysis as the outcome. Cardiovascular endpoint events in CKD patients included coronary artery disease, chronic coronary artery disease, valvular heart disease, myocardial disease, arrhythmia, extracorporeal defibrillation, cerebrovascular disease, and peripheral vascular disease according to the Kidney Disease: Improving Global Outcomes 2012 clinical practice guideline (11). The time of the events was from the beginning of hemodialysis treatment to the first onset of cardiovascular events. Data were collected from the hemodialysis centers until May 31, 2020.

Development and validation of the prediction model

Marker selection

Variables with a missing amount of more than 50% were not included in this study and the remaining variables were filled with the mean value within the group. Two steps were involved for marker selection. First, 3 methods (stepwise logistic regression, hypothesis testing (Student's *t*-test for normal parameters, Wilcoxon-Mann-Whitney test for non-normal parameters, and χ^2 -test for categorical variables), and the nomogram) were applied separately for all parameters. Parameters that met 1 condition (stepwise logistic regression $P < 0.05$, hypothesis testing, $P < 0.05$, or hazard ratio $> 50\%$ in the nomogram) were screened out for further selection. Second, all possible combinations among the selected parameters were used to construct numerous Cox proportional hazards models. The final optimal parameter set was determined by balancing the number of parameters and the model's performance [primarily based on the value of the Harrell's concordance index (C-index)] (Figure 1).

Model construction and validation

On the basis of the optimized parameters and using multivariate regression analysis, the Cox proportional hazards model was built. Kaplan-Meier estimates were used to generate survival curves. The regression coefficient for each covariate could be converted to a hazard ratio, which was used to construct the nomogram.

The area under the receiver operating characteristic curve (AUROC) was calculated to evaluate the performance of the risk-prediction models. The predictive accuracy and discriminative ability of the nomogram were determined by C-index and the calibration curve. The C-index indicates the consistency between the predicted results and the actual results. Calibration was performed by comparing the means of predicted survival with those of actual survival.

Furthermore, considering no independent validation sets in the present study, 10-fold cross-validation and hold-out validation (70% training and 30% validation, repeated 100 times) were used to validate the reliability of our model (Figure 1).

Statistical analysis

Student's *t*-test (for normal parameters), Wilcoxon-Mann-Whitney test (for non-normal parameters), and χ^2 -test (for categorical variables) were used for comparisons between 2 groups. Statistical significance was set at $P < 0.05$. Survival curves were generated according to the Kaplan-Meier method. Multivariate analyses were performed using the Cox proportional hazards model. Cox regression coefficients were used to generate a nomogram.

R (version 4.0.3, <https://www.r-project.org/>) was used for data analysis and figure plotting in the study. R is a language and environment for statistical computing and graphics. It was initially written by Robert Gentleman and Ross Ihaka of the Statistics Department of the University of Auckland. The home page address is <https://www.r-project.org/>. Nomogram and calibration plots were generated using the *rms* (version 6.0-1, written by Frank Harrell, <https://CRAN.R-project.org/package=rms>) package. Cox proportional hazards model and C-index were generated using the *survival* (version 3.2-7, written by Terry M. Therneau, *et al.*, <https://CRAN.R-project.org/package=survival>) package. AUROCs were calculated using the *survivalROC* (version 1.0.3, written by Patrick J. Heagerty, <https://CRAN.R-project.org/package=survivalROC>) and *timeROC* (version 0.4, written by Paul Blanche, <https://CRAN.R-project.org/package=timeROC>) package.

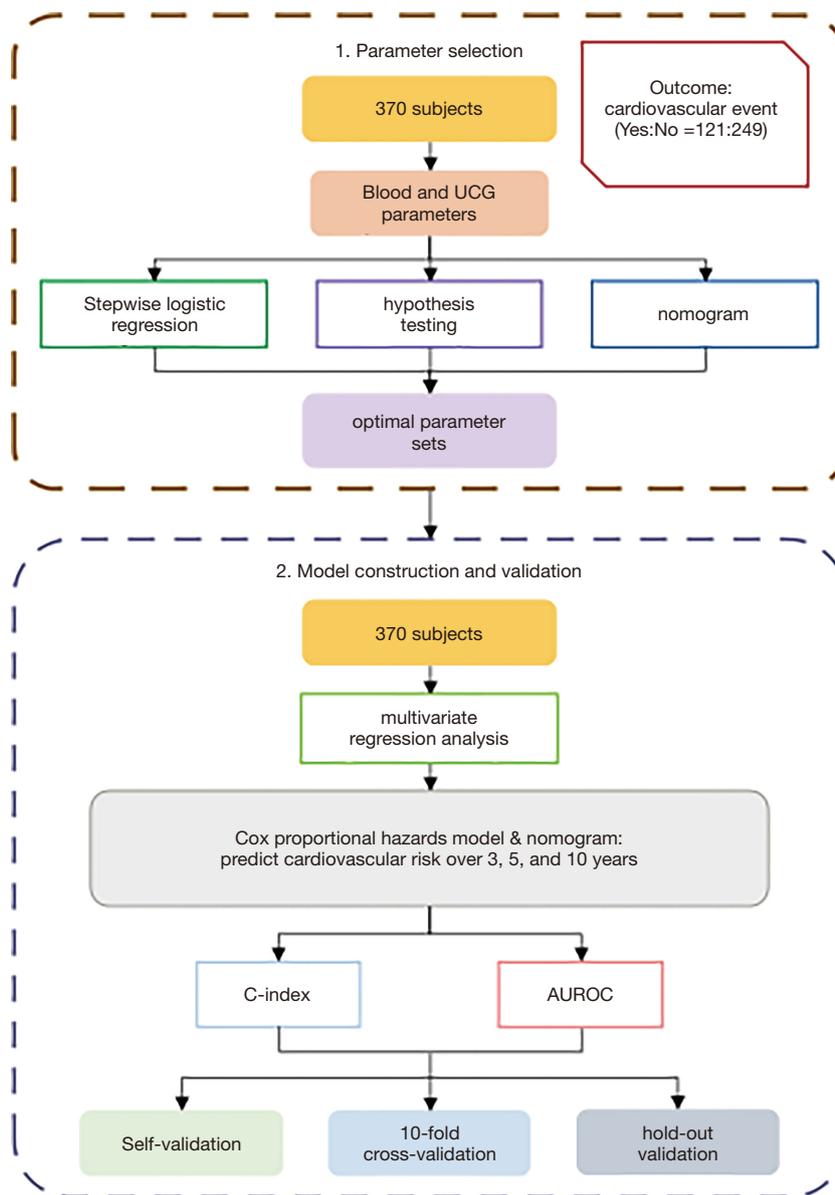


Figure 1 Flowchart of the study design. In step 1 of parameter set selection, stepwise logistic regression, hypothesis testing, and nomogram were used jointly for preselection, and the final set was determined from all possible combinations. In step 2 of model construction and validation, a Cox proportional hazards model coupled with a nomogram were constructed using the optimal parameter set and multivariate regression analysis. Then, Self-validation, 10-fold cross-validation, and hold-out validation (70% training and 30% validation, repeated 100 times) were used to verify the reliability and accuracy of the model with C-index and AUROC.

Results

Basic characteristics of the participants

A total of 370 patients with hemodialysis were involved in the present study. A total of 121 patients (32.7%) had a first cardiovascular event and 249 (67.3%) did not have any

cardiovascular events. Patients with cardiovascular events were older and were more likely to have hypertension and DM. Their FER, CRP, WBC, GLU, and CK-MB levels were higher and their CRE levels were lower than those of patients with no cardiovascular events. UCG inspection results indicated that the values of LAD, RVD,

IVST, LVPWT, A, and E/A were higher in patients with cardiovascular events and the values of EF and E were lower (Table 1).

Optimal parameter set selection

Two steps were conducted for optimal parameter set selection. After the first step, 20 of the 42 parameters were preselected by stepwise logistic regression, hypothesis testing, and nomogram as follows: hypertension, DM, age, FER, phosphate, TG, CRP, WBC, NEUT, CRE, GLU, CK-MB, LAD, RVD, IVST, LVPWT, EF, E, A, and E/A. In the second step, all possible parameter combinations among them were used to construct numerous Cox proportional hazards models. Eight parameters were finally selected, balancing the number of parameters used and the values of the C-index. The optimal parameter set consisted of hypertension, DM, age, phosphate, TG, CRP, WBC, and IVST.

Model construction

A Cox proportional hazards model was constructed using the optimal parameter set. The nomogram was constructed from the hazard ratio converted by the coefficients for each covariate to predict the probability of cardiovascular events among long-term hemodialysis patients (Figure 2). Each variable was assigned a score (ranging from 0 to 100) and a total point (ranging from 0 to 300) that was calculated for each patient. Furthermore, the sum risk scores were converted to predict 3-year, 5-year, and 10-year risk of a cardiovascular events.

The calibration curve showed good agreement between predicted and observed outcomes for the cardiovascular event prediction model (Figure 3A,B,C). The C-index of the nomogram was 0.808 [95% confidence interval (CI): 0.773–0.844]. The AUROCs for predicting 3-, 5- and 10-year cardiovascular event risk were 0.836, 0.845, and 0.869, respectively (Figure 3D). The time-dependent AUROCs and the 95% CI of the nomogram at various time points are shown in Figure 3E. As expected, our model performed well in predicting cardiovascular event occurrence.

Model validation

Two methods, 10-fold cross-validation and hold-out validation (70% training and 30% validation, repeated 100 times), were used to validate the reliability of our

model. For the 10-fold cross-validation, the mean of the C-indexes was 0.794, and the time-dependent AUROCs for predicting 3-, 5-, and 10-year cardiovascular events were 0.832, 0.832, and 0.845, respectively (Figure 4A). For the hold-out validation, the mean of the C-indexes was 0.798, and the time-dependent AUROCs for predicting 3-, 5-, and 10-year cardiovascular events were 0.822, 0.832, and 0.860, respectively (Figure 4B). Both validation methods demonstrated satisfactory predictive ability of our cardiovascular event prediction model.

Discussion

In the present study, we developed a Cox proportional hazards model and a nomogram for long-term hemodialysis patients to predict the risk of cardiovascular event occurrence. A total of 8 indicators (hypertension, DM, age, phosphate, TG, CRP, WBC, and IVST) were included in the model. Self-validation, 10-fold cross-validation, and hold-out validation all verified the reliability and accuracy of our model with high C-indexes and AUROCs. Therefore, our model is particularly valuable for clinically identifying high-risk hemodialysis patients and facilitating the development of personalized patient care. It can also be used as a basis for further research on cardioprotective hemodialysis strategies.

It has been confirmed that cardiovascular events are the leading cause of death in long-term hemodialysis patients (4). In 1999, the FRS was developed to predict the rate of cardiovascular events in the general population in 10 years (5). It reported that smoking, hypertension, DM, advanced age, elevated TC, elevated LDL, and reduced HDL were the major independent risk factors. long-term hemodialysis may lead to changes in pathophysiology, including anemia, microinflammatory state, water and sodium retention, calcium and phosphorus metabolism disorders, malnutrition, etc. these factors may interact with each other, and may affect the cardiovascular system, leading to hypertension, coronary heart disease, arrhythmia, cerebrovascular accident, congestive heart failure, and other cardiovascular diseases (12). Various studies on cardiovascular risk factors in dialysis patients have since been published, and several risk-prediction methods constructed (10,13-17). Serum phosphorus (13,18-20), calcium (10,19,20), WBC (21,22), CRP (10,16,23,24), and albumin (7,10,13,17) levels were also considered common risk predictors of cardiovascular events. In our study, we used 8 indicators (hypertension, DM, age, phosphate, TG,

Table 1 Clinical and demographical characteristics of hemodialysis patients with chronic kidney disease

Characteristic	All (n=370)	No cardiovascular event group (n=249)	Cardiovascular event group (n=121)	P value
First cardiovascular event time (month)	40.65±36.42	46.59±37.71	28.43±30.28	<0.001*
Hypertension (no/yes)	84:286	74:175	10:111	<0.001*
DM (no/yes)	239:131	184:65	55:66	<0.001*
Sex (male/female)	214:156	140:109	74:47	0.430
Age (years)	59.37±14.95	54.94±14.13	68.49±12.27	<0.001*
PCT (µg/L)	13.22±94.69	14.16±103.84	11.29±72.69	0.991
iPTH (pg/mL)	433.25±402.10	451.78±413.41	395.10±376.55	0.188
FER (ng/mL)	453.06±643.55	391.41±418.15	579.93±942.37	0.048*
Phosphate (mmol/L)	1.88±0.68	1.87±0.63	1.89±0.78	0.777
TC (mmol/L)	4.44±1.36	4.46±1.36	4.40±1.39	0.610
TG (mmol/L)	1.78±1.34	1.87±1.46	1.60±1.03	0.210
HDL (mmol/L)	1.09±0.37	1.07±0.35	1.12±0.42	0.294
LDL (mmol/L)	2.56±1.07	2.55±1.04	2.59±1.13	0.831
APOA (g/L)	1.17±0.23	1.19±0.22	1.13±0.25	0.054
APOB (g/L)	0.99±0.32	1.00±0.33	0.96±0.30	0.111
CRP (mg/L)	15.40±33.07	10.78±22.32	24.91±46.88	<0.001*
WBC (10 ⁹ /L)	7.01±2.87	6.59±2.25	7.87±3.70	0.002*
HB (g/L)	96.36±22.91	96.56±23.89	95.94±20.84	0.892
PLT count (10 ⁹ /L)	205.82±75.84	201.83±73.42	214.02±80.30	0.221
NEUT (10 ⁹ /L)	5.45±13.98	5.33±16.01	5.69±8.43	0.056
LYMPH (10 ⁹ /L)	3.20±11.93	2.94±10.99	3.74±13.68	0.998
CRE (µmol/L)	840.66±415.84	870.49±441.19	779.26±351.85	0.036*
BUN (mmol/L)	23.24±10.56	23.18±10.47	23.37±10.80	0.947
Calcium (mmol/L)	2.17±0.30	2.17±0.27	2.16±0.35	0.166
UA (µmol/L)	496.42±142.50	498.05±144.74	493.05±138.30	0.635
GLU (mmol/L)	7.01±3.88	6.74±3.92	7.55±3.77	0.004*
UIBC (µmol/L)	29.09±30.32	29.67±35.81	27.90±13.20	0.785
TIBC (µmol/L)	38.97±17.67	38.61±8.79	39.71±28.29	0.129
CK-MB (ng/mL)	14.37±16.29	12.67±9.29	17.85±24.89	<0.001*

Table 1 (continued)

Table 1 (continued)

Characteristic	All (n=370)	No cardiovascular event group (n=249)	Cardiovascular event group (n=121)	P value
eGFR (mL/min)	20.14±97.68	22.52±97.78	15.25±97.71	0.117
AORD (mm)	27.85±3.25	27.98±2.88	27.60±3.90	0.579
LAD (mm)	35.01±4.94	34.55±4.74	35.95±5.21	0.007*
RVD (mm)	22.62±4.67	21.82±4.23	24.26±5.11	<0.001*
IVST (mm)	12.43±2.28	12.00±1.60	13.30±3.09	<0.001*
LVEDD (mm)	45.39±9.29	45.92±7.92	44.31±11.58	0.401
LVPWT (mm)	12.36±9.10	11.44±7.66	14.25±11.31	<0.001*
MPAD (mm)	20.72±4.46	20.55±4.02	21.08±5.26	0.309
EF (%)	64.94±6.39	65.73±6.15	63.33±6.59	<0.001*
FS (%)	38.99±13.54	37.96±12.42	41.10±15.44	0.466
E (cm/s)	0.75±0.23	0.77±0.23	0.73±0.25	0.015*
A (cm/s)	0.91±0.20	0.90±0.19	0.94±0.23	0.008*
E/A	0.89±0.66	0.88±0.31	0.89±1.07	<0.001*

Values are expressed as mean ± standard deviation. P value was determined by comparing characteristics of individuals with no cardiovascular events with those with cardiovascular events and evaluated using the Wilcoxon-Mann-Whitney test or χ^2 -test. Text with * indicates significant $P < 0.05$. A, mitral valve peak A velocity; AORD, aortic root diameter; APOA, apolipoprotein A; APOB, apolipoprotein B; BUN, blood urea nitrogen; CK-MB, creatine kinase MB; CRE, creatinine; CRP, C-reactive protein; DM, diabetes mellitus; E, mitral valve peak E velocity; EF, ejection fraction; eGFR, estimated glomerular filtration rate; E/A, ratio of E and A; FER, serum ferritin; FS, left ventricular fraction shortening; GLU, blood glucose; HB, hemoglobin; HDL, high-density lipoprotein cholesterol; iPTH, intact parathyroid hormone; IVST, interventricular septum thickness; LAD, left atrium diameter; LDL, low-density lipoprotein cholesterol; LVEDD, left ventricular end-diastolic diameter; LVPWT, left ventricular posterior wall thickness; LYMPH, lymphocyte absolute value; MPAD, main pulmonary artery diameter; NEUT, neutrophil absolute value; PCT, biochemical measurements of procalcitonin; PLT, platelet count; RVD, right ventricle diameter; TC, total cholesterol; TG, triglyceride; TIBC, total iron-binding capacity; UA, uric acid; UIBC, unsaturated iron-binding capacity; WBC, white blood cells.

CRP, WBC, and IVST) to establish our risk-prediction model. Most of our parameters were strongly associated cardiovascular event risk, supporting the findings of previously published studies and indicating the reliability of our model. We also used UCG relative indicators in the present study and found that IVST was a good predictor. This is one of the strengths of our study. Many studies have indicated that combining serological indicators with imaging indicators can improve diagnostic performance (25-28). Other advantages of this study are as follows. First, all the parameters involved in this research can be obtained from routine medical examinations and are not restricted by medical conditions. Even with poor clinical practice and

medical resources, the indicators we chose are affordable. Second, our nomogram model not only had a satisfactory performance but also allowed the visual tracking of the risk assessment. It does not require complex calculations and is fairly straightforward for clinicians and patients to understand. Finally, the 2-step parameter selection strategy was used to ensure that indicators reached their full prediction potential. First carried on the parameter pre-selection using multiple methods (stepwise logistic regression, hypothesis testing, and nomogram) and then compared the results of all possible parameter combinations, which was time consuming but necessary.

However, our study also has some limitations. First, the

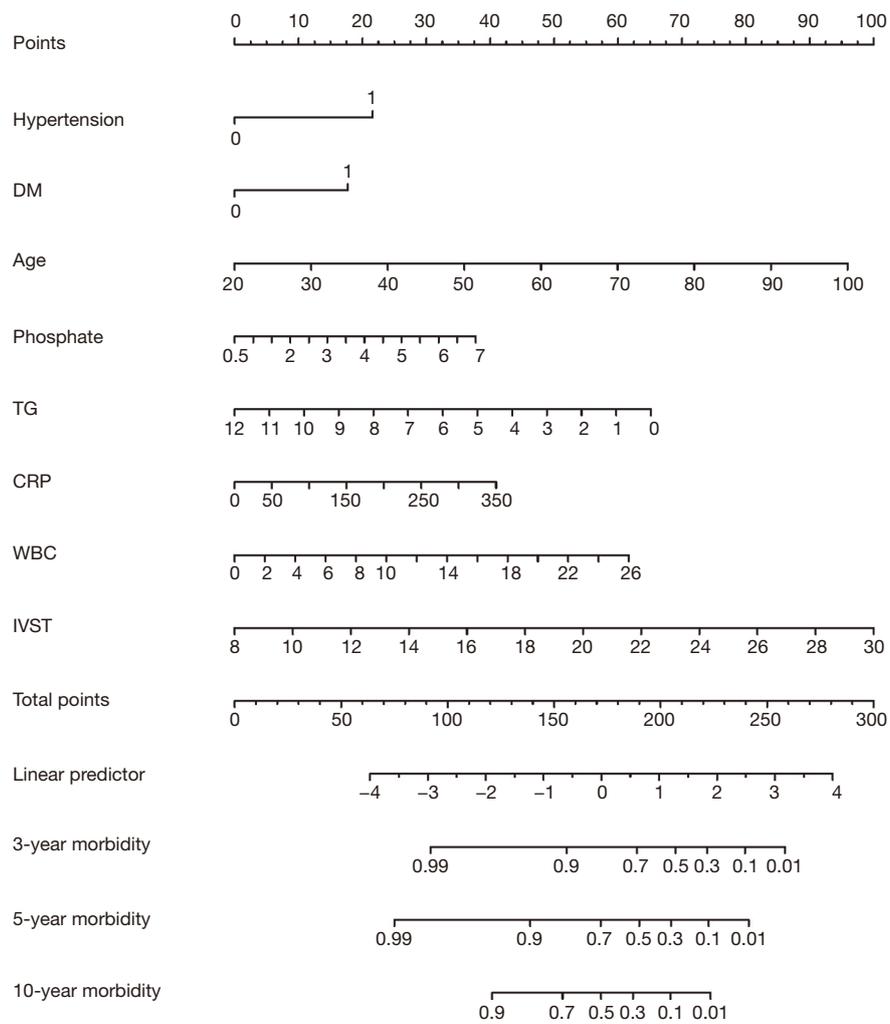


Figure 2 Nomogram for the risk prediction of cardiovascular events in hemodialysis patients. Length of each variable axis in the nomogram varies. First, draw a line upward to determine the score of each variable in the points axis. Second, find the location of the sum scores of these variables in the total points axis. Finally, draw a line down to the morbidity axes to determine the possibility of 3-, 5- or 10-year cardiovascular event occurrence risk.

prediction model was designed for renal failure patients on hemodialysis. Whether non-renal failure and irregular dialysis patients were suitable for this model was not clear and requires further validation. Second, the present study was based on Chinese patients. Further validation with diverse populations and races is essential. Finally, the present study was a cross-sectional study and longitudinal studies are needed to further validate the reproducibility of the current findings and the application value of our model in cardiovascular event risk prediction.

In conclusion, our nomogram model constructed from non-invasive conventional serological and UCG parameters was found to accurately predict individual cardiovascular event risk in hemodialysis patients. In clinical practice, this model can be used to identify high-risk individuals for more precise and efficient personalized management and treatment. In view of the poor prognosis of long-term hemodialysis in patients with end-stage renal disease, it is expected to carry out further research on renal prognosis and death in the future.

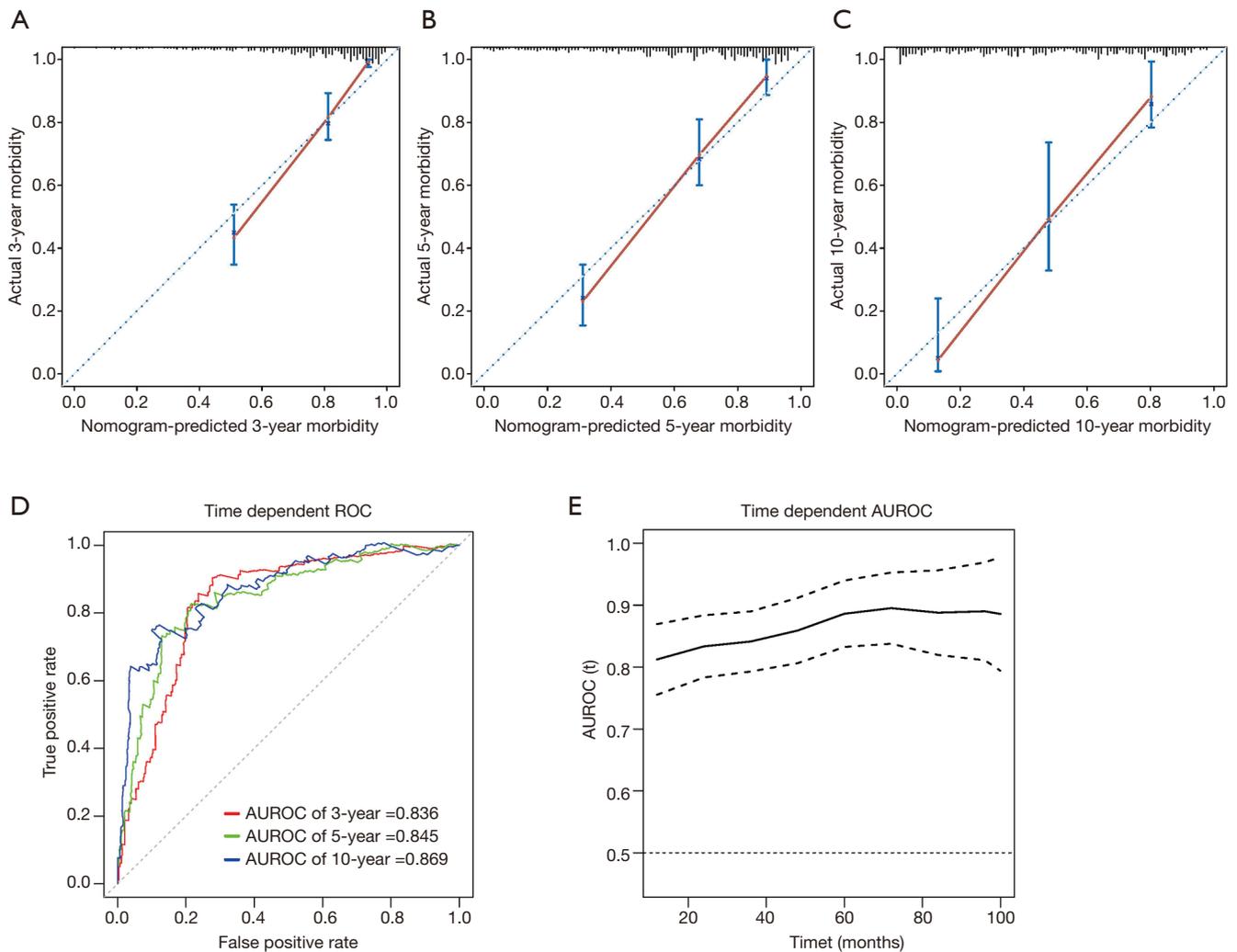


Figure 3 Performance of the nomogram in the risk assessment of cardiovascular events in hemodialysis patients. (A-C) Calibration curve of the nomogram. X-axis represents the nomogram-predicted morbidity and the y-axis represents actual morbidity; 95% confidence intervals (CIs) were measured by Kaplan-Meier analysis. (D) Time-dependent receiver-operating characteristic (ROC) curves of cardiovascular event risk prediction in 3 (red), 5 (green), and 10 (blue) years. (E) Line graph of the time-dependent area under the receiver-operating characteristic curve (AUROC; solid line) and its 95% CI (dashed lines) for cardiovascular event risk prediction.

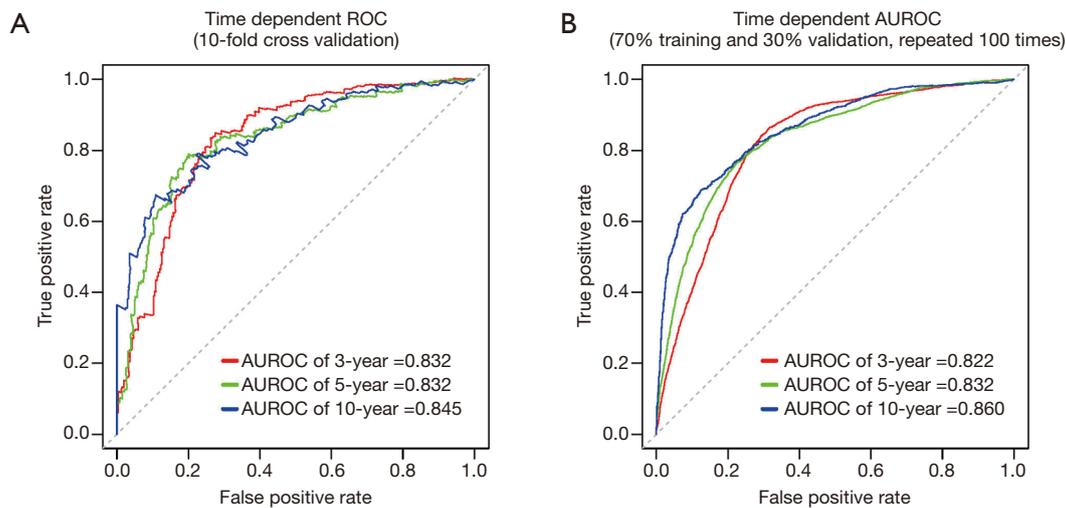


Figure 4 Validation of the nomogram in the risk assessment of cardiovascular events in hemodialysis patients. (A) Time-dependent ROC curves in 3 (red), 5 (green), and 10 (blue) years using 10-fold cross-validation. (B) Time-dependent ROC curves in 3 (red), 5 (green), and 10 (blue) years using hold-out validation (70% training and 30% validation, repeated 100 times).

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/apm-21-286>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the institutional review board of the Third Affiliated Hospital of Southern Medical University and the Third Affiliated Hospital of Sun Yat-sen University. All participants provided informed written consent before participating in the study. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

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