Development and Validation of a Nomogram for Predicting the 6-Month Survival Rate in Incident Hemodialysis Patients

Guode Li

Maoming People's Hospital

linsen Jiang

The Second Affiliated Hospital of Soochow University

Jiangpeng Li

The Second Affiliated Hospital of Soochow University

huaying shen

The Second Affiliated Hospital of Soochow University

Shan Jiang

The Second Affiliated Hospital of Soochow University

Han Ouyang (✉ ouyanghan198784@aliyun.com)

The Second Affiliated Hospital of Soochow University

kai song

The Second Affiliated Hospital of Soochow University

Research Article

Keywords: hemodialysis, nomogram, prediction model, survival, all-cause mortality

Posted Date: November 29th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1053111/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background

The all-cause mortality in hemodialysis(HD) patients is higher than in the general population and the first 6 months after initiating dialysis is an important transitional period for new HD patients. The aim of this study was to develop and validate a nomogram for predicting the 6-month survival rate among HD patients.

Methods

We developed a prediction model based on a training cohort of 679 HD patients. Multivariate Cox regression analyses were performed to identify predictive factors, followed by establishment of a nomogram. Next, performance of the nomogram was assessed using the C-index and calibration plots. The nomogram was validated through applying discrimination and calibration to an additional cohort of 173 HD patients.

Results

During a follow-up period of six months, there were 47 and 12 deaths in the training cohort and validation cohort, respectively, with a mortality rate of 7.3% and 6.9%, respectively. The score included five commonly available predictors: age, temporary dialysis catheter, intradialytic hypotension, use of ACEi or ARB, and use of loop diuretics. The score revealed good discrimination in the training cohort [C-index 0.775(0.693-0.857)] and validation cohort [C-index 0.758(0.677-0.836)], whereas the calibration plots showed good calibration, indicating suitable performance of the nomogram model. The total score point was then divided into two risk classifications: low risk (0-90 points) and high risk (≥ 91 points). Results showed that all-cause mortality was significantly different in HD patients in the high-risk group compared to the low-risk group.

Conclusions

This nomogram can accurately predict the 6-month survival rate for HD patients, and thus it can be used in clinical decision-making.

Introduction

The mortality of dialysis patients is still relatively high despite the large amount of resources devoted to treat patients with end-stage renal disease (ESRD). Specifically, the all-cause mortality in dialysis patients is about seven times higher than in the general population (1). A previous study found that the mortality of hemodialysis (HD) patients was higher in the first year, especially within the first three months after

dialysis initiation (2). Data from European and American national databases has revealed that the mortality of HD patients within 90 days after initiation of dialysis ranges between 5.6% and 8.6%, whereas the mortality within one year is between 16.2% and 24.3% (2). Furthermore, patients who succumbed within 90 days after dialysis initiation accounted for 35–50% of deaths within one year (3).

The first three months after initiating dialysis is an important transitional period for new dialysis patients. Studies have reported that early death of HD patients is often defined as death within three months after the beginning of dialysis (4). However, only few studies have focused on the mortality of HD patients within six months. Although early mortality in HD patients is not negligible and seriously affects the prognosis of patients, clinical risk prediction models for predicting the 3- or 6-month survival rate are lacking.

Risk prediction model, a mathematical model for predicting the probability of end-point events, has been widely used in the medical field, such as the EuroSCORE II model for predicting the risk of heart surgery and the Charlson Comorbidity Index (CCI) for predicting survival of cancer patients (5, 6). The use of nomogram to predict all-cause mortality or cardiovascular mortality in dialysis patients has achieved good application value and is easy to implement (7, 8). Herein, we aimed at developing and validating an easy-to-use nomogram for predicting the 6-month survival rate among HD patients.

Methods

Patients

This study enrolled 679 adult HD patients at the Second Affiliated Hospital of Soochow University in China from 31st January 2009 to 31st December 2013. The exclusion criteria were as follows: (1) under the age of 18 years, (2) history of kidney transplantation, (3) chronic peritoneal dialysis (PD), and (4) comorbid with malignant tumor. After excluding the ineligible patients, a total of 643 subjects were enrolled in the study. In addition, we included a validation cohort comprising 173 adult ESRD patients who underwent dialysis at another independent dialysis center between 31st January 2016 and 31st May 2020. The study protocol was approved by the Clinical Research Ethics Committee of The Second Affiliated Hospital of Soochow University and is registered in the Chinese Clinical Trial Registry (NO. ChiCTR 1900024999). Notably, signed informed consent was obtained from all participants prior to the study.

Clinical and laboratory parameters

The following laboratory parameters were recorded: creatinine (Cr), hemoglobin (HB), albumin (Alb), blood urea nitrogen (BUN), serum uric acid (UA), calcium (Ca), phosphorus (P), potassium (K), low-density lipoprotein cholesterol (LDL), total triglycerides (TG), total cholesterol (TC), parathyroid hormone (PTH), high-sensitivity C-reactive protein (Hs-CRP), total Kt/V, and residual kidney function (RKF). RKF was estimated from mean values of creatinine clearance and urea clearance. The Kt/V results were obtained using the special hemodialysis formula of Kt/V.

Candidate variables

Demographic variables such as age, smoking, and gender were included as candidate variables, whereas blood pressure, height, and dialysis dry weight were included as physical examination variables. In addition, concurrent disease, including diabetes, hypertension, cerebrovascular disease, and cardiovascular disease were included. All data were obtained within one month after the patient's regular HD reached dry body mass. Body mass index (BMI) was calculated according to the height and weight, whereas hypertension was based on at least two separate blood pressure measurements $\geq 130/80$ mmHg. The chronic kidney disease stages were categorized according to the Kidney Disease Outcomes Quality Initiative (KDOQI) HD clinical practice guidelines (9). Intradialytic hypotension was determined as follows: systolic blood pressure drop was greater than 20 mmHg or mean arterial pressure (MAP) drop was greater than 10 mmHg during dialysis treatment. The associated symptoms of hypotension were also recorded.

Follow-up and outcome

Patients in the training and validation cohorts were followed for six months after initiating HD treatment. The outcome of interest was all-cause mortality which was defined as death due to cardiovascular disease, cerebrovascular disease, infectious disease, multiple organ failure, secondary malignant neoplasms, and other reasons. All patients were followed up until death, transfer to PD treatment, undergoing a renal transplant, or transfer to another dialysis center.

Statistical analysis

All statistical analyses were performed using the SPSS software (version 23.0) and R software (version 3.6.2). Continuous variables were presented as mean $\pm$ SD and compared using Kruskal-Wallis test, when appropriate. Categorical variables were presented as proportions and compared using a χ^2 test. All candidate variables ($p < 0.30$) were then subjected to backward elimination for multivariable logistic regression analysis. Backward elimination started with all candidate predictors and ran a sequence of tests to remove or keep variables in the model based on $p < 0.05$ for variable exclusion. In addition, the hazard ratio and the 95% confidence interval (95% CI) were calculated. $P < 0.05$ was considered statistically significant for all tests.

Univariate survival analyses of the grouping variates were performed using Kaplan-Meier curve with log-rank test. On the other hand, multivariable analysis was performed using Cox regression models to develop a nomogram. Next, the predictive performance of the nomograms was evaluated using the C-index. Calibration was performed through bootstrapping with 1000 research resamples and assessed using calibration plots, which measured the relationship between predicted probabilities and observed proportions. Decision curve analysis (DCA) was conducted to determine the clinical usefulness of the survival nomogram by quantifying the net benefits at different threshold probabilities in the cohort. Furthermore, patients were categorized into 'low' or 'high' risk groups using recursive partitioning tree

analysis to generate the optimum cut-off point. Finally, Kaplan-Meier curves were plotted for the two risk groups.

Results

Baseline characteristics

The baseline characteristics of the two groups are summarized in **Table 1**. Patients in the training and validation cohorts had similar demographic characteristics, comorbidities, laboratory data, medicine use, and outcomes (**Table 1**). During a follow-up of 6 months, there were 47 (7.3%) and 12 (6.9%) deaths in the training cohort and validation cohort, respectively. Fourteen (29.79%) deaths in the training cohort were attributed to cardiovascular diseases. **Figure 1** shows the detailed causes of death.

Results of the selection of variables

In the training cohort, univariate analysis found eight candidate predictors that were closely associated with the all-cause mortality (**Table 1**), including “age”, “platelet”, “White blood cells”, “temporary dialysis catheter”, “intradialytic hypotension”, “LDL”, “use of ACEi or ARB”, and “use loop of diuretics”. After multivariable Cox regressive analysis, five predictors were left for inclusion in the final multivariable model (**Table 2**): “age”, “temporary dialysis catheter”, “intradialytic hypotension”, “use of ACEi or ARB”, and “use of loop diuretics”. Finally, we used a nomogram to develop a score for survival prediction based on these five predictors (**Fig 2**).

Nomogram for predicting survival

Multivariable Cox regression and hazard ratios (HR) were calculated for the prognostic factors used to establish the nomogram (**Table 2**). In the training cohort, increasing age, temporary dialysis catheter, intradialytic hypotension, use of ACEi or ARB, and use of loop diuretics were associated with survival from all causes after follow-up for 6 months. The linear predictors obtained from the Cox regression model were used to develop the nomogram for predicting survival in HD patients (**Fig 2**).

Validation of the nomogram

The performance of the model in the training and validation cohorts was assessed using discrimination and calibration. The score revealed good discrimination in the training cohort [C-index 0.775(0.693-0.857)] and validation cohort [C-index 0.758(0.677-0.836)], and the calibration plots showed good calibration (**Fig 3,4**). The model appeared to be well-calibrated, and indicated a good fit of the predicted probabilities and observed proportions. Based on the five predictors, we used the nomogram to develop a score for predicting the survival probability. The total possible points for the score ranged from 0 to 186 according to the classification and regression tree model. Next, patients were divided into two survival risk levels: low risk (0 - 90 points) and high risk (≥ 91 points). Finally, Kaplan-Meier curves were plotted for these two risk groups (**Fig 5,6**).

Clinical utility

The DCA of the nomograms is presented in **Fig 7**. The net benefit was calculated by adding the true positives and subtracting the false positives. The straight line represents the assumption that all patients will die, whereas the horizontal line represents the assumption that no patient will die. The DCA demonstrated that the nomogram added more net benefit compared to the treat-all strategy or treat-none strategy with a threshold probability $\geq 5\%$.

Discussion

The Dialysis Outcomes and Practice Pattern Study (DOPPS) study conducted in 11 countries showed that the highest mortality of HD patients was observed in the first month after dialysis initiation (10). It is well documented that the mortality of HD patients is higher within three to six months after dialysis initiation. According to the United States Renal Data System (USRDS) report (1), all-cause mortality peaked about two months after dialysis initiation in HD patients. Therefore, the high mortality rate of dialysis patients in the early stage of HD should not be ignored. This study developed and validated a model for predicting all-cause mortality risk among incident HD patients using five easily available baseline variables, with the overarching goal of informing patients about their future risk up to six months.

The five predictors were: age, temporary dialysis catheter, intradialytic hypotension, use of ACEi or ARB, and use of loop diuretics. Notably, they included traditional death risk factors and dialysis-related factors. The easy and calculable score described here was designed to identify HD patients who were at high risk of death during the first six months after initiating dialysis. This model would not only identify patients' risk factors for early death, but would also help health care workers to make targeted treatment measures in advance. Identifying death risk factors for dialysis patients in early stage can help initiate earlier interventions for those at risk, which include, but are not limited to, management of hypertension and hypotension, choice of the dialysis pathway, and strategies for the use of ACEi or ARB or diuretics in different populations.

In this study, multivariable analysis was performed using Cox regression models. Results showed that age was an independent risk factor for death in HD patients, with every one-year increase in age resulting in a concomitant 3% increase in the risk of death in dialysis patients. Given that elderly patients are prone to complicated complications with poor body resistance and cognitive decline, their quality of life decreases and mortality increases after initiation of dialysis(11). In particular, elderly HD patients who lived alone and did not have caregivers during or after the HD treatment had a higher risk of death. Therefore, elderly HD patients should be given special care by doctors and nurses as well as social welfare institutions.

Results also showed that patients who received temporary dialysis catheter had a higher risk of death compared to those who used arteriovenous fistula (AVF) to perform dialysis treatment. Previous studies have shown that the risk of death in patients using temporary dialysis catheter is 1.43 times higher than in HD patients who use AVF at the initial stage of dialysis (12). It is worth noting that the increased risk of

death associated with temporary dialysis catheter may be caused by unplanned and delayed dialysis treatment, or associated with catheter-related infections. Studies have shown that about 13.3% of patients using dialysis catheters have positive blood culture results, and the risk of blood-borne infection in catheter patients is three times higher than in AVF patients (13). Therefore, effective evaluation of vascular conditions in HD patients before dialysis, preparation for establishment of dialysis pathway in advance, and increasing the proportion of AVF in the initial treatment may reduce the risk of death.

A previous study found that hypertension was one of the risk factors for predicting 3-year all-cause mortality in HD patients, which was caused by the increased incidence of cardiovascular and cerebrovascular diseases in dialysis patients (14). However, in this study we found that patients with intradialytic hypotension had a lower mortality compared to patients with normal or hypertension in the first six months after initiating dialysis. It has previously been reported that intradialytic hypotension is a common complication of HD patients, which may be associated with decreased blood volume, autonomic nervous dysfunction, cardiac dysfunction, and vascular dysfunction during dialysis (15). Notably, severe intradialytic hypotension may cause arrhythmia, occlusion of AVF, and shorter dialysis times. Many clinical studies have found that the occurrence of intradialytic hypotension can increase the risk of death in HD patients (16, 17). Results obtained in this study also found that intradialytic hypotension is a risk factor for death in HD patients, thus, clinicians should pay enough attention to this clinical complication.

Gamboa *et al.* (18) reported that the use of ACEi or ARB can inhibit the microinflammatory state in HD patients. Another study also found that application of ACEi or ARB in HD patients has different degrees of efficacy in hemodynamics, cardiovascular remodeling, cardiovascular events, all-cause death, and other aspects (19). Therefore, ACEi or ARB is one of the most commonly used antihypertensive drugs in HD patients. However, we found that HD patients using ACEi or ARB had a lower 6-month survival rate, which is an interesting finding with two probable causes. First, the use of ACEi or ARB may cause the occurrence of hypotension during dialysis which can lead to increased mortality in HD patients. Second, the use of ACEi or ARB is a common cause of hyperkalemia in dialysis patients, which is a risk factor of cardiovascular death in HD patients.

It has been reported that continued use of loop diuretics during the first year of dialysis is associated with lower hospitalization rates, lower intradialytic hypotension rates, and lower interdialysis weight gain, but it had no effect on mortality (20). Herein, results showed that continued use of loop diuretics after HD treatment can reduce the risk of death within six months. In addition to increasing urine output, loop diuretics can improve sodium excretion by about 20% and is unaffected by the levels of glomerular filtration rate (GFR) (21). It is well known that better volume control and urinary sodium excretion are beneficial to fluid overload. Moreover, urinary potassium excretion allows the patient to eat more freely, which can improve the quality of life of dialysis patients. Therefore, loop diuretics are the most commonly used and most effective in patients with ESKD. The findings of this study also recommend the use of loop diuretics in dialysis patients in the first six months.

However, this study had some limitations. First, the sample size was small, which may increase the possibility of type II errors. Notably, only variables with univariate analysis results of $P < 0.05$ were selected for Cox analysis, which to some extent lost the related risk factors affecting death. Therefore, a larger sample size study should be conducted to confirm our findings. Second, although the robustness of our nomogram was subjected to extensive internal validation using bootstrap testing, the universality was uncertain for other HD patients. Thus, external assessment should be conducted in wider HD populations.

Conclusions

This study developed and validated a nomogram with good accuracy for predicting 6-month survival in HD patients. The simple and reliable score was designed to identify HD patients who were at high risk of death. Results suggested that treating hypotension, increasing the frequency of potassium detection and blood pressure monitoring during ACEi or ARB treatment, and increasing the use of diuretics may be the key points to reduce all-cause mortality risk for HD patients in the first six months after HD initiation. Furthermore, it is possible to improve the survival rate by reducing the use of temporary dialysis catheter, and the planned establishment of AVF prior to dialysis is advocated.

Declarations

Ethics approval and consent to participate

The Ethics Committee of the Second Affiliated Hospital of Soochow University approved this study, and all methods were performed in accordance with the guidelines and regulations of the Ethics Committee and is registered in the Chinese Clinical Trial Registry (NO. ChiCTR 1900024999). Notably, signed informed consent was obtained from all participants prior to the study.

Consent for publication

Not applicable.

Availability of data and materials

The data used in this study are available from the corresponding author upon request.

Competing interests

The authors declare no conflict of interest.

Funding

This work was partially supported by the National Natural Science Pre-Research Fund of the Second Affiliated Hospital of Soochow University (SDFEYGJ1702).

Authors' contributions

All authors contributed to the study design, data analysis, article writing, and revision, and agree to take responsibility for the results.

Acknowledgment

Guode Li, Linsen Jiang, and Jiangpeng Li contributed equally to this study.

References

1. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2018 Annual Data Report: epidemiology of kidney disease in the United States. *Am J Kidney Dis.* 2019, 73 (3S1): A7-A8.
2. Yazawa M, Kido R, Ohira S, et al. Correction: early mortality was highly and strongly associated with functional status in incident Japanese hemodialysis patients: a cohort study of the large national dialysis registry. *PLoS One.* 2016, 11(12): e0168811.
3. Noordzij M, Jager KJ. Increased mortality early after dialysis initiation: a universal phenomenon. *Kidney Int.* 2014, 85(1): 12-14.
4. Gómez de la Torre-Del Carpio Andrea, Bocanegra-Jesús Alejandra, Guinetti-Ortiz Katia, et al. Early mortality in patients with chronic kidney disease who started emergency haemodialysis in a Peruvian population: Incidence and risk factors. *Nefrologia.* 2018, 38(4), 425-432.
5. Maloof MA. Learning when data sets are imbalanced and when costs are unequal and unknown. Washington, DC: In Proceedings of the ICML'03 Workshop on Learning from Imbalanced Data Sets, 2003.
6. Wang J, Zhao P, Hois CH. Costsensitive online classification. *IEEE Transactions on Knowledge and Data Engineering.* 2014, 26(10):2425-2438.
7. Xia X, Zhao C, Luo Q, et al. Nomogram for Predicting Cardiovascular Mortality in Incident Peritoneal Dialysis Patients: An Observational Study. *Sci Rep.* 2017,7(1)13889.
8. Anker SD, Gillespie IA, Eckardt KU, et al. Development and validation of cardiovascular risk scores for haemodialysis patients. *Int J Cardiol.* 2016, 216, 68–77.
9. Daugirdas J, Depner T. In Reply to 'Hypotension and Frequent Hemodialysis: Clarification Requested Regarding the KDOQI Hemodialysis Adequacy Guideline 2015 Update'. *Am J Kidney Dis.* 2016, 67(3):532.
10. Robinson BM, Zhang J, Morgenstern H, et al. Worldwide, mortality risk is high soon after initiation of hemodialysis. *Kidney Int.* 2014, 85(1): 158-165.
11. Song Yu-Huan, Cai Guang-Yan, Xiao Yue-Fei, et al. Risk factors for mortality in elderly haemodialysis patients: a systematic review and meta-analysis. *BMC Nephrol.* 2020, 21(1), 377.
12. Roca-Tey R, Arcos E, Comas J, et al. Starting hemodialysis with catheter and mortality risk: persistent association in a competing risk analysis. *J Vasc Access.* 2016, 17(1): 20-28.

13. Xue H, Ix JH, Wang W, et al. Hemodialysis access usage patterns in the incident dialysis year and associated catheter -related complications. *Am J Kidney Dis.* 2013, 61(1): 123 -130.
14. Jing zhu, Tang chao, Han ouyang, et al. Prediction of All-Cause Mortality Using an Echocardiography-Based Risk Score in Hemodialysis Patients. *Cardiorenal Med.* 2020.
15. Rocha A, Sousa C, Teles P, et al. Effect of Dialysis Day on Intradialytic Hypotension Risk. *Kidney Blood Press Res.* 2016, 41(2):168-174.
16. McIntyre CW, Goldsmith DJ. Ischemic brain injury in hemodialysis patients: which is more dangerous, hypertension or intradialytic hypotension?. *Kidney Int.* 2015, 87(6):1109-1115.
17. Doshi M, Murray PT. Approach to intradialytic hypotension in intensive care unit patients with acute renal failure. *Artif Organs.* 2015, 27(9):772-780.
18. Gamboa JL, Pretorius M, Todd-Tzanetos DR, et al. Comparative effects of angiotensin-converting enzyme inhibition and angiotensin-receptor blockade on inflammation during hemodialysis. *Am Soc Nephrol.* 2012, 23(2): 334-342.
19. Young JB, Dunlap ME, Pfeffer MA, et al. Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials .*Circulation.* 2004, 110: 2618-26.
20. Sibbel Scott, Walker Adam G, Colson Carey, et al. Association of Continuation of Loop Diuretics at Hemodialysis Initiation with Clinical Outcomes. *Clin J Am Soc Nephrol.* 2018,14(1), 95-102.
21. Tanaka Misa, Oida Emi, Nomura Keiko, et al. The Na⁺-excreting efficacy of indapamide in combination with furosemide in massive edema. *Clin Exp Nephrol.* 2005, 9(2), 122-6.

Tables

Due to technical limitations, tables are only available as a download in the Supplemental Files section.

Figures

The causes of death

Figure 1

Different causes of death in hemodialysis patients.

Figure 2

Nomogram to predict risk of all-cause mortality in HD patients.

Figure 3

Calibration plots of training cohort for predicting probability of all-cause mortality. A diagonal line indicates perfect calibration.

Figure 4

Calibration plots of validation cohort for predicting probability of all-cause mortality.

Figure 5

Kaplan-Meier survival curves in the training cohort on the basis of the nomogram.

Figure 6

Kaplan-Meier survival curves in the validation cohort on the basis of the nomogram.

Figure 7

Decision curve analysis for the survival nomogram.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [table1docx.pdf](#)
- [Table2docx.pdf](#)