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ORIGINAL RESEARCH

Prognostic Value of Systemic Inflammatory Response Index for the Prognosis of Diabetic Maintenance Hemodialysis Patients: A Retrospective Observational Study

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Background: The systemic inflammatory response index (SIRI) had been identified as an inflammatory marker and has been linked to determining clinical outcomes in several diseases. We advocated the relationship between the initial SIRI and the prognosis of diabetic maintenance hemodialysis (MHD) patients.

Methods: A total of 153 diabetic MHD patients who accepted regular HD treatment at our hospital were enrolled in this study. SIRI was calculated as neutrophil × monocyte/lymphocyte. All patients were separated into two groups based on the levels of SIRI. LASSO regression and Cox regression analyses were then made to determine the prognostic value of SIRI for diabetic MHD patients.

Results: During a median 33-month follow-up period, 50 (32.7%) patients died. The higher SIRI value (≥ 2.5) had a higher risk of death (adjusted HR=4.00, 95% CI 1.77–9.07, P=0.001) after adjusting for other confounding clinical features. The devised nomogram ground on SIRI value and clinical features had great predictive value for overall survival in diabetic MHD patients. The nomogram proved both prominent calibration competence and therapeutic subservience.

Conclusion: SIRI is a relatively excellent predictor for OS, and the suggested nomogram ground on SIRI leads to an accurate prediction value for diabetic MHD patients.

Keywords: systemic inflammatory response index, maintenance hemodialysis, diabetes, nomograms, prognosis

Introduction

As one of the most common and serious microvascular complications of diabetes, diabetes kidney disease (DKD) has become the central cause of end-stage kidney disease (ESKD), thus the need for renal replacement therapy (RRT) has increased rapidly in the past decades.[1,2] Despite the great improvement in the knowledge and facilities, maintenance hemodialysis (MHD) patients, especially patients with diabetes, continue to be associated with a high rate of poor clinical outcomes as well as expensive medical healthcare costs.[3,4] Therefore, doctors must prioritize identifying patients at high risk of death for diabetic MHD patients applying biomarkers or prediction algorithms to manage these patients effectively and improve the prognosis of them.

Inflammation plays an important role in the onset, development, and prognosis of patients with kidney disease, and thus, several inflammation-based markers have been set up for the diagnosis and prognosis of these patients.[5–8] Nevertheless, previous studies have also demonstrated that the systemic inflammatory response index (SIRI), which was calculated as neutrophil × monocyte / lymphocyte count, might reflect the inflammation status, and have predictive value for the diagnosis and prognosis of different diseases.[9–12] Moreover, A recent study showed that SIRI was a promising biomarker of mortality for PD patients.[13] However, the association between SIRI and the prognosis of

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diabetic MHD patients were not been investigated. Therefore, the aim of this study was to discuss the connection between initial SIRI and the prognosis of diabetic MHD patients. We then constructed a nomogram merging SIRI and other clinical features to investigate the prognosis of diabetic MHD patients.

Materials and Methods

Selection of Participants

All patients in this retrospective study were collected from the first People's Hospital of jiangxia district of Wuhan City between January 1, 2014, to December 1, 2019. We included patients who were aged 18 or older at the time of HD therapy and underwent MHD for greater than 3 months, and clinically or pathologically diagnosed DKD patients who had a clear outcome during the follow-up (continue MHD, transfer to peritoneal dialysis or renal transplantation, died). The exclusion criteria included: incomplete data or unclear medical history, transferred from peritoneal dialysis or a history of renal transplantation; patients with acute or chronic infection, malignant tumors, and hematological diseases.

This study was conducted according to the Declaration of Helsinki and the Ethics Committee of the first People's Hospital of jiangxia district of Wuhan City agrees to this study (No. 2021024) and the informed consent was waived considering the confidentiality of patients' information.

Finally, a total of 153 patients were included in this study, including 85 males (55.6%) and 68 females (44.4%), with an average age of 64.3 ±10.7 (34–89) years old (Figure 1).

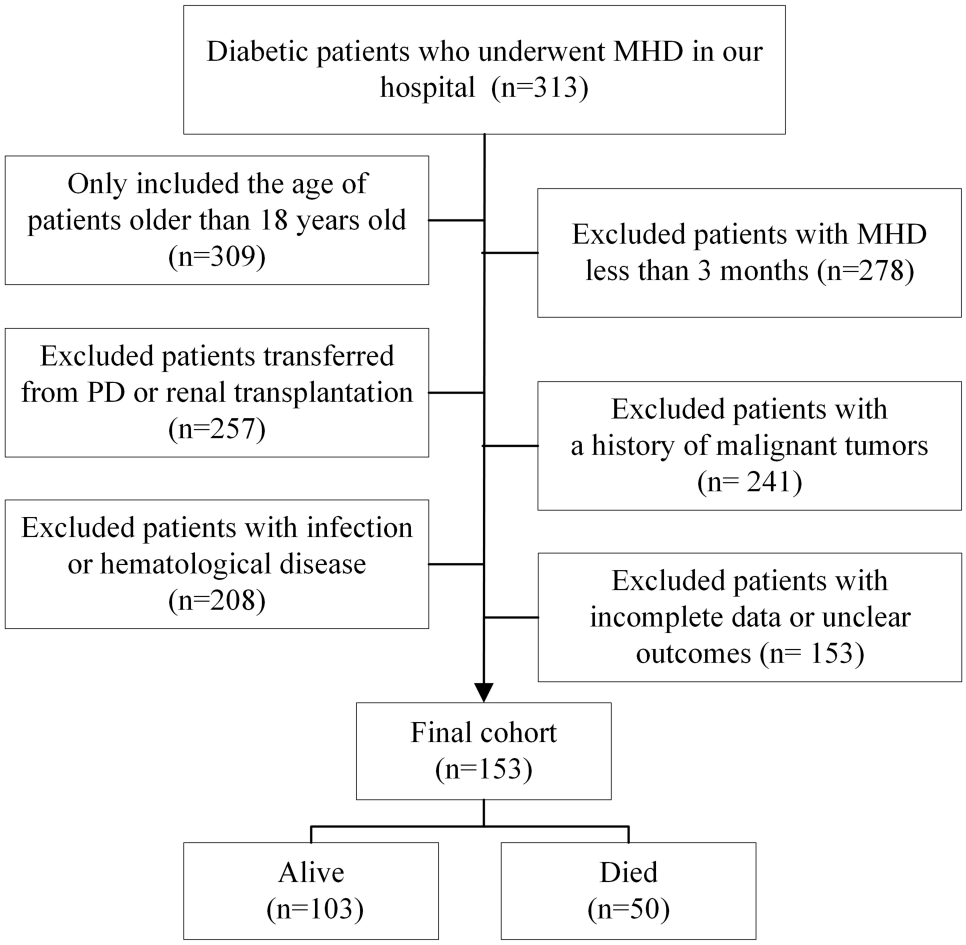

Figure 1 The flow chart of this study.

Data Collection

All variables were collected in the first 3 months of MHD treatment in our hospital. Demographic data included age, sex, body mass index (BMI), complications (hypertension, cardiovascular disease, cerebrovascular disease), marital status, education status, vascular access, and the duration of diabetes. All baseline laboratory data including complete blood count were obtained from nonfasting predialysis patients on a midweek day and analyzed using a standardized process.

SIRI was calculated as neutrophil × monocyte / lymphocyte. The estimated glomerular filtration rate (eGFR) was computed by the latest creatinine measurements formerly dialysis according to the CKD-EPI formula.[14] Cardiovascular disease (CVD) was considered as one of the following: coronary heart disease, congestive heart failure, cerebrovascular infarcts or hemorrhage, peripheral vascular disease, and sudden cardiac death.[15] Cerebrovascular disease was considered as one of the following: hemorrhagic or ischemic stroke, transient ischemic attacks, subarachnoid hemorrhage, and intracranial aneurysm.

Outcomes

All patients in this study were followed up via clinic visits or telephone interviews. The primary end-out point was the overall survival (OS). All patients were followed up until death or December 31, 2022.

Statistical Analysis

All analysis was conducted by R (version 4.1.0) software. The X-tile software was utilized to assure the optimal cutoff value of SIRI. And the least absolute shrinkage and selection operator (LASSO) regression was used for the selection of significant factors for OS in diabetic MHD patients. Multivariable Cox analysis was then used to construct a nomogram for the prognosis of diabetic MHD patients. The predictive performance of the predictive nomogram for OS was assessed using the area under the receiver operating characteristic curves (AUC), and calibration plots as well as decision curve analysis (DCA). A value of $P < 0.05$ was considered significant.

Results

Characteristics of All Patients

Finally, 153 patients were included in this study altogether, including 85 males (55.6%) and 68 females (44.4%), with an average age of 64.3 ± 10.7 (34–89) years old. All patients fell into two groups by the SIRI value (2.5) according to the X-tile (Figure 2). The baseline information was given in Table 1.

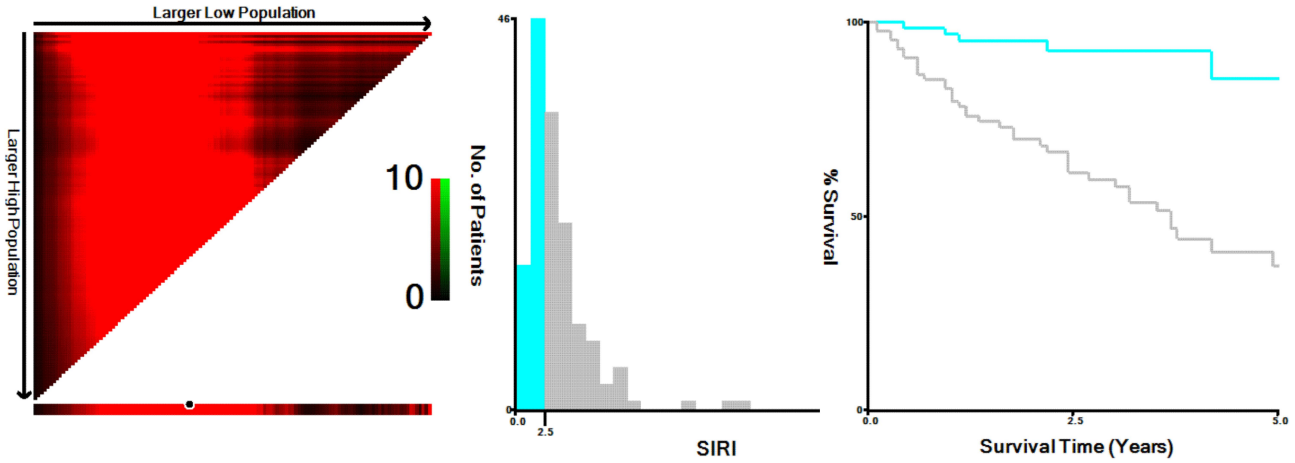

Figure 2 X-tile analyses of SIRI to obtain the optimal cutoff value of SIRI. X-tile plots for patients with diabetic MHD are shown on the left panels; the black circles indicate the optimal cutoff values, which are also presented in histograms (middle panels). Kaplan-Meier curves are shown in the right panels.

Table 1 The Baseline Characteristics of All Patients

Characteristics	SIRI < 2.5 (n=68)	SIRI ≥ 2.5 (n=85)	P value
Age, years old	62.9 ± 10.1	65.4 ± 11.0	0.147
Gender, Male, n (%)	42 (61.8)	43 (50.6)	0.169
BMI, kg/m2	22.7 ± 4.7	22.4 ± 3.8	0.674
Martial status, n (%)			0.653
Married	63 (92.6)	77 (90.6)	
Unmarried/others	5 (7.4)	8 (9.4)	
Education status			0.914
Primary school or below	31 (45.6)	39 (44.7)	
Middle school or above	37 (54.4)	47 (55.3)	
Vascular access			0.145
AVF	18 (26.5)	32 (37.6)	
TCC	50 (73.5)	53 (62.4)	
DM duration, n (%)			0.010
>10 years	26 (38.2)	49 (57.6)	
≤ 10 years	42 (61.8)	36 (42.4)	
Complications			
Hypertension, n (%)	64 (94.1)	74 (87.1)	0.146
CVD, n (%)	20 (29.4)	25 (29.4)	1.000
Cerebrovascular disease, n (%)	9 (13.2)	19 (22.4)	0.149
Laboratory results			
Systolic blood pressure, mmHg	144.0 ± 20.2	148.6 ± 23.5	0.201
Diastolic blood pressure, mmHg	82.0 ± 12.3	81.5 ± 11.6	0.194
White blood cells,×109/L	9.2 ± 3.7	7.7 ± 2.8	0.035
Hemoglobin, g/L	90.7 ± 20.5	91.4 ± 23.7	0.837
Red blood cells, ×1012/L	3.2 ± 0.6	3.3 ± 0.8	0.565
MCV, fL	90.3 ± 5.6	89.0 ± 7.8	0.246
MCH, pg	27.9 ± 2.3	27.8 ± 3.2	0.734
MCHC, g/L	310.7 ± 16.6	307.6 ± 38.7	0.537
RDW, %	15.5 ± 5.8	15.9 ± 5.2	0.150
Platelets, ×109/L	200.2 ± 57.5	196.7 ± 34.4	0.781
SIRI	1.5 ± 0.6	6.3 ± 1.8	<0.001
Glucose, mmol/L	8.9 ± 2.6	9.2 ± 3.3	0.781
HbA1c, %	7.1 ± 1.7	7.1 ± 1.5	0.920
Albumin, g/L	37.8 ± 4.7	35.6 ± 5.3	0.008
BUN, mmol/L	23.3 ± 10.4	26.1 ± 9.4	0.080
Creatinine, umol/L	822.2 ± 173.7	831.0 ± 184.1	0.841
eGFR, mL/min	7.6 ± 1.9	5.8 ± 2.0	0.158
Total cholesterol, mmol/L	4.4 ± 1.3	4.3 ± 1.1	0.591
Triglyceride, mmol/L	1.7 ± 0.5	1.8 ± 0.6	0.814
HDL-C, mmol/L	1.2 ± 0.4	1.1 ± 0.4	0.184
LDL-C, mmol/L	2.2 ± 0.9	2.1 ± 0.8	0.673
Serum ferritin, ug/L	217.9 ± 74.2	168.1 ± 61.3	0.209
CRP, mg/L	7.0 ± 2.9	8.5 ± 2.1	0.348
Potassium, mmol/L	4.2 ± 0.8	4.1 ± 0.7	0.442
Sodium, mmol/L	138.0 ± 3.0	137.7 ± 3.1	0.512
Calcium, mmol/L	2.1 ± 0.2	2.1 ± 0.3	0.419
Serum phosphorus, mmol/L	1.5 ± 0.4	2.2 ± 0.5	0.028
Parathyroid Hormone, pg/mL	205.0 ± 81.2	204.0 ± 78.0	0.998
Survival months	26.0 (15.0, 45.0)	23.0 (13.0, 44.0)	0.502
Death, n (%)	7 (10.3)	43 (50.6)	<0.001

Abbreviations: SIRI, systemic inflammatory response index, BMI, body mass index, AVF, arteriovenous fistula, TCC, tunneled central venous catheter, DM, diabetes mellitus, CVD, cardiovascular disease, MCV, mean corpuscular volume, MCH, mean corpuscular hemoglobin, MCHC, mean corpuscular hemoglobin concentration, RDW, red cell distribution width, HbA1c, hemoglobin A1c, BUN, blood urea nitrogen, eGFR, estimated glomerular filtration rate, HDL-C, High-density lipoprotein cholesterol, LDL-C, Low-density lipoprotein cholesterol, CRP, C reactive protein.

The Association Between SIRI and OS for Patients with MHD

Each patient's SIRI measurement was displayed in Figure 3A. Based on the cut-off value (2.5), patients were split into a high-risk group and a low-risk group (Figure 4A–C). The AUC of SIRI for OS was 0.782 (95% CI 0.725–0.854, Figure 4D). DCA demonstrated that SIRI was clinically helpful (Figure 4E). The high-SIRI group had a worse prognosis for patients with MHD than the lower-SIRI group (Figure 4F, P<0.0001).

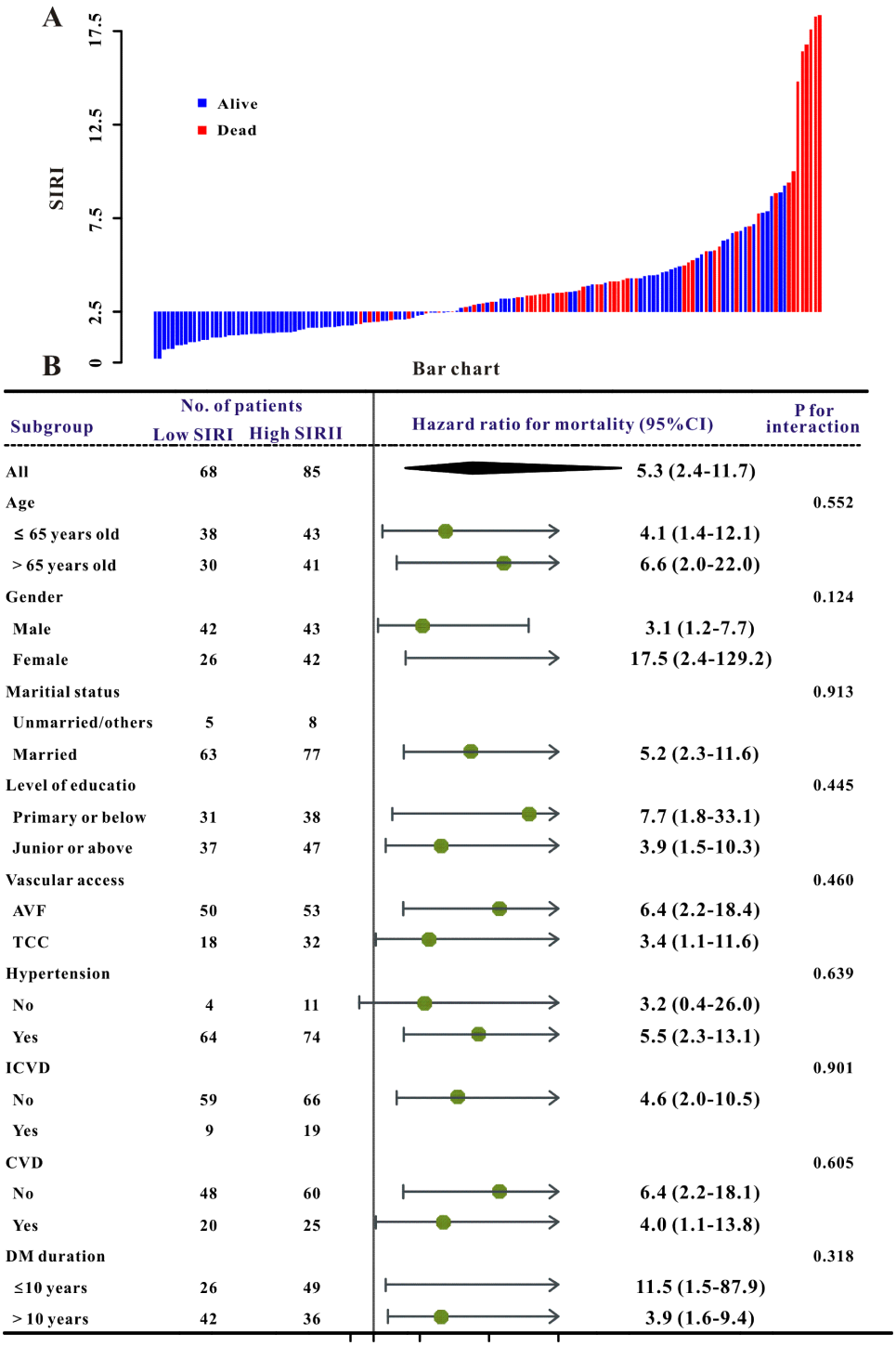

Figure 3 The waterfall plots and forest plots of the high-SIRI group and low-SIRI group for the prognosis of diabetic MHD patients. The waterfall plot of SIRI for each patient of mortality (**A**) and the subgroup analysis of the SIRI for the prognosis of individuals with diabetic MHD patients (**B**).

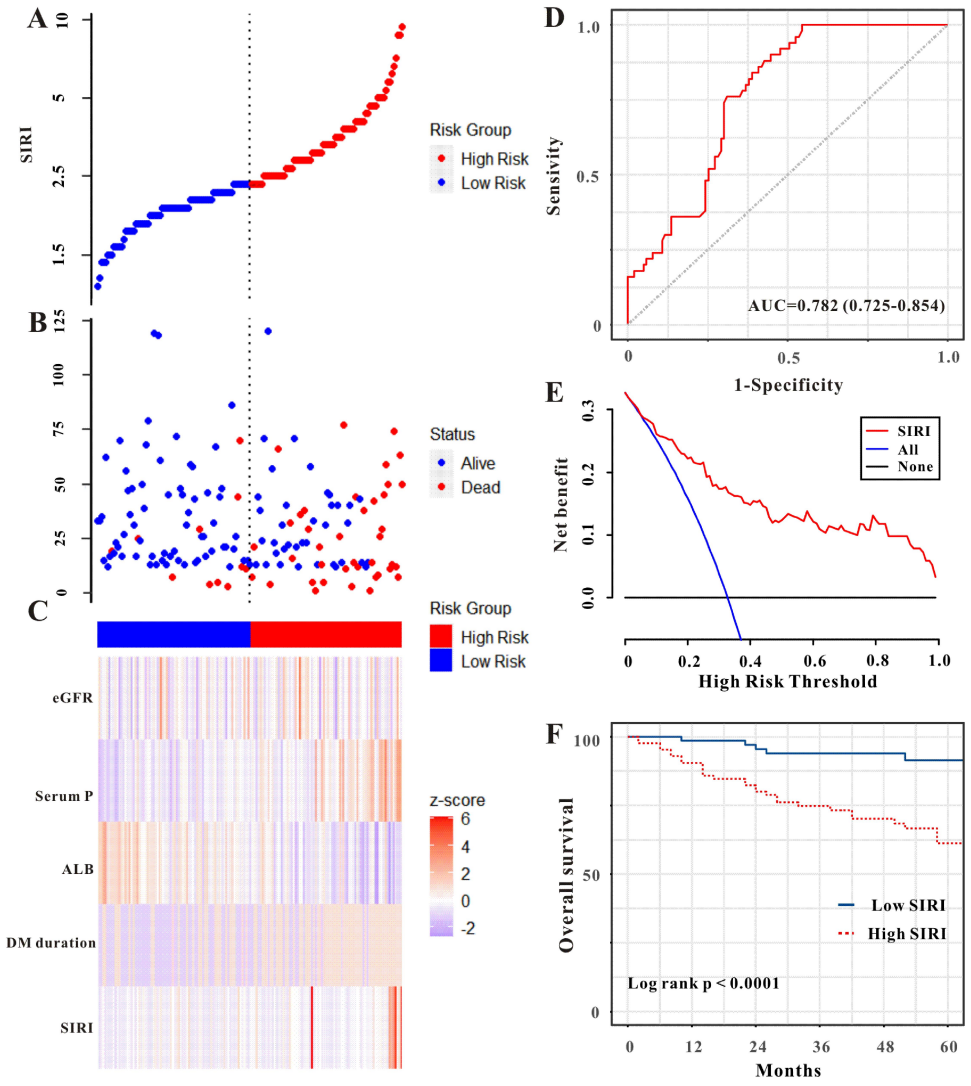

Figure 4 The SIRI was established to detect the overall mortality of patients with diabetic MHD. All patients were distinguished into high and low risk based on the SIRI (**A**), the relationship between survival time and prognosis of patients in the two corresponding groups (**B**), and the heatmap of other markers between the two groups (**C**). Receiver operating characteristic (ROC) curve analysis of the SIRI for overall mortality (**D**), Decision curve analysis of the risk score for the overall mortality (**E**). Kaplan-Meier curves show the overall mortality of groups with different risks (**F**).

During a median 33-month follow-up period, 50 (32.7%) patients died, the high-SIRI patients had a higher risk of mortality even after adjusting for other variables (Table 2). And patients with SIRI < 2.5 had a lower risk of mortality than those with SIRI ≥ 2.5 group in almost all subgroups (Figure 3B).

Development and Verification of the Predictive Nomogram

LASSO regression for OS demonstrated that seven risk factors were finally included in this study (Figure 5A and B). Moreover, multivariable Cox analysis was then used to build a nomogram for OS in diabetic MHD patients. As shown in Table 2, DM duration, eGFR, serum albumin, serum phosphate, and SIRI were finally included in this nomogram (Figure 6A).

Furthermore, the 1-, 3-, and 5-year AUC of the predictive nomogram for OS was 0.701 (95% CI 0.613–0.809), 0.759 (95% CI 0.678–0.841), and 0.847 (95% CI 0.768–0.906), respectively (Figure 6D). The calibration curves also demonstrated a great agreement between predicted OS and actual OS (Figure 6B). Furthermore, DCA demonstrated that the predictive nomogram was helpful for decision-making (Figure 6C).

Table 2 Univariate and Multivariate Cox Regression Analysis for All-Cause Mortality

	Univariate		Multivariate	
	HR (95% CI)	**P**	**HR (95% CI)**	**P**
SIRI ≥ 2.5	5.26 (2.37–11.71)	<0.001	4.00 (1.77–9.07)	0.001
DM duration				
≥ 10 years	2.29 (1.23–4.26)	<0.001	1.69 (1.18–2.64)	0.025
< 10 years	Ref.	–	Ref.	–
MCV	0.95 (0.92–0.99)	0.013	0.97 (0.94–1.01)	0.120
BUN	1.00 (0.97–1.03)	0.874		
eGFR	0.89 (0.75–0.94)	<0.001	0.94 (0.89–0.99)	0.038
Albumin	0.92 (0.87–0.97)	0.003	0.93 (0.88–0.96)	0.010
Serum phosphorus	2.05 (1.45–2.89)	<0.001	1.78 (1.26–2.51)	0.001

Abbreviations: SIRI, systemic inflammatory response index, DM, diabetes mellitus, MCV, mean corpuscular volume, BUN, blood urea nitrogen, eGFR, estimated glomerular filtration rate, HR, hazard ratio, 95% CI, 95% confidence index.

Discussion

In this study, we found a robust association between SIRI and prognosis for diabetic MHD patients. And the predictive nomogram based on SIRI and other clinical features exhibited great calibration, discrimination, and clinically useful. Thus, SIRI was a reliable prognostic marker for diabetic MHD patients, and the suggested nomogram based on SIRI leads to an accurate prediction for diabetic MHD patients.

DM is currently the leading cause of ESKD in many countries as well as in China, and the ones with DM are known to have the worst clinical outcomes in patients with MHD. The reason for this phenomenon is partly at least for the underlying metabolic disturbances, such as oxidative stress and inflammation, and so on. Yen et al retrospectively collected 212 diabetic MHD patients and found that the 1.5-year OS rate was 85.7%.[16] Recently, an observational study that included 263 diabetic MHD patients demonstrated that the 1-, and 5-year OS rates were 90.9%, and 53.9%, respectively.[17] Similar to these studies, in this study, we included patients in our hospital and found that the 1-, and 5-year OS rates for diabetic MHD patients were 86.9%, and 67.3%, respectively. Therefore, a reliable and novel predictor or model for the prognosis of diabetic MHD patients for the clinicians to risk stratification and then timely and effective therapies might be taken to improve the prognosis of these patients and lead to lower healthcare costs.

SIRI is one of the most effective inflammatory markers based on the complete blood count and the association between SIRI and clinical outcomes had been found in previous studies with different diseases. Using the data from the MIMIC-III database, Zhang et al calculated the levels of different inflammatory indicators and concluded that SIRI was

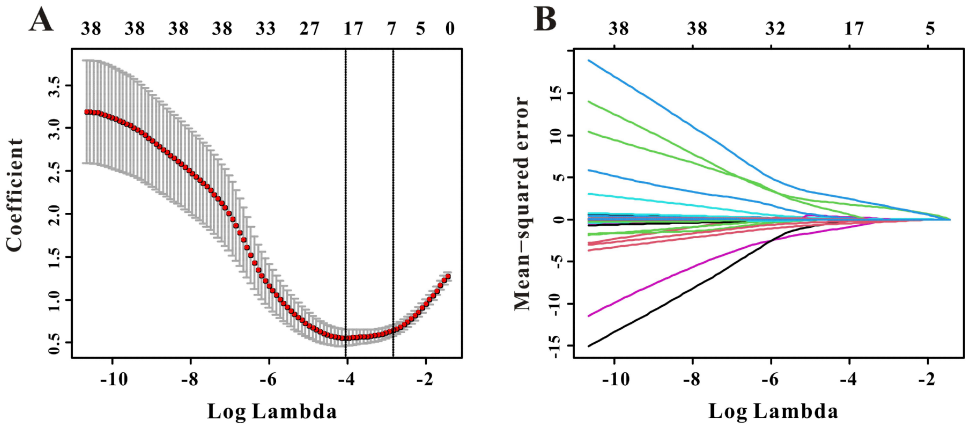

Figure 5 Selection of significant factors associated with OS in diabetic MHD patients by LASSO Cox regression model. (**A**) The selection process of the optimum value of the parameter λ in the Lasso regression model by cross-validation method; (**B**) the variation characteristics of the coefficient of variables.

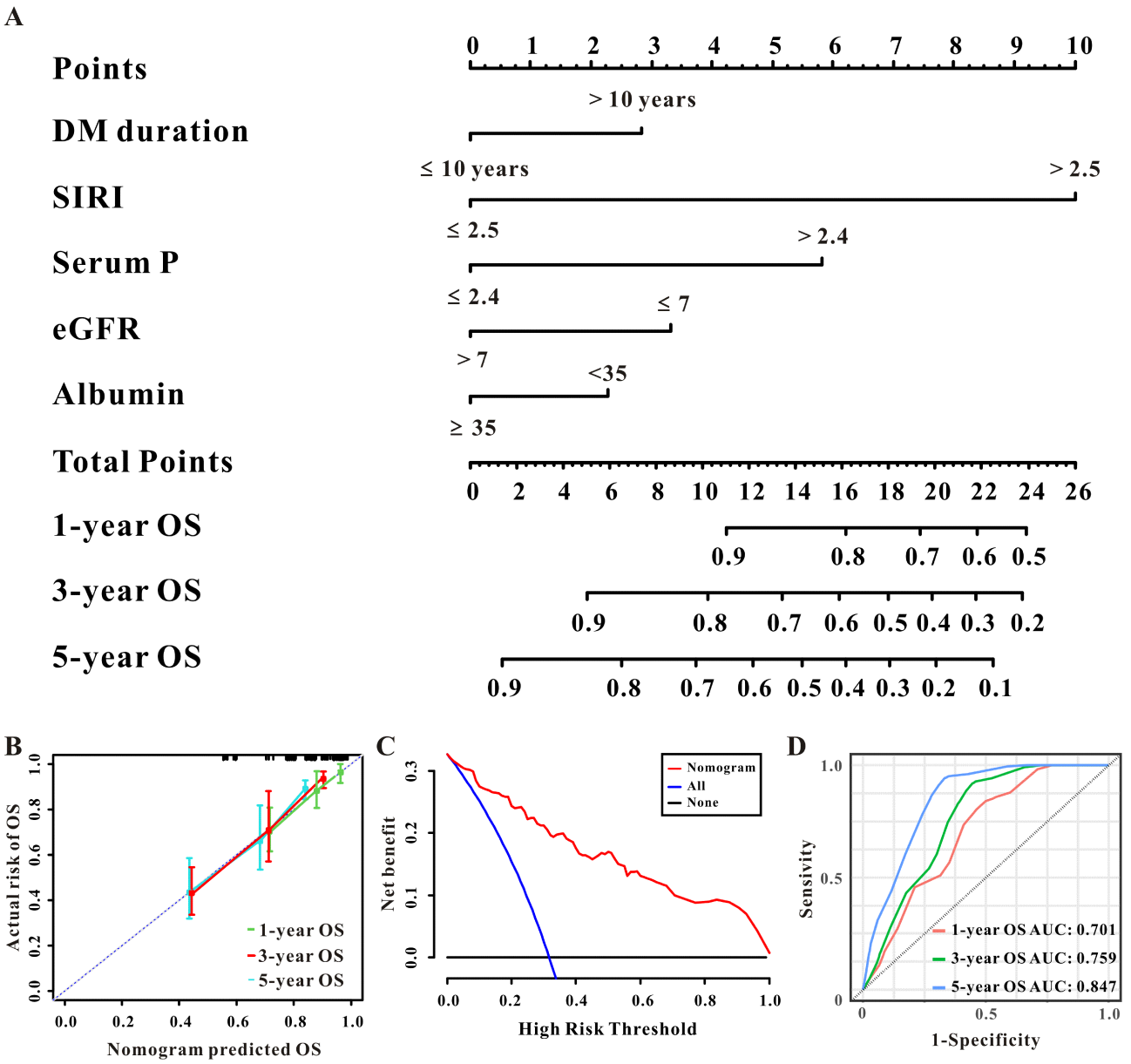

Figure 6 The established nomogram for OS in patients with diabetic MHD (**A**), the 1-year, 3-year, and 5-year calibration curves of the nomogram for OS (**B**), decision curve analysis of the nomogram for OS (**C**), and the time-dependent ROC curves for the 1-year, 3-year, and 5-year OS in patients with diabetic MHD (**D**).

a good marker for stroke patients.[11] Similar results had also been demonstrated in patients with acute ischemic stroke and laryngeal squamous cell carcinoma.[10,18] As for renal diseases, SIRI could also have prognostic value for patients with renal cell carcinoma in previous studies.[9,19] Moreover, a recent study also found that SIRI could serve as a novel and efficient indicator for the early diagnosis of catheter-related bloodstream infection in patients undergoing MHD.[20] However, as far as we know, this is the first study to explore the association between initial SIRI and prognosis of diabetic MHD patients and we demonstrated that SIRI could be a great marker for OS of them.

As we all know that inflammation plays an important role in the onset, development, and prognosis of patients with CKD or ESKD.[8] White blood cells and subtypes are the most common and easy-to-use methods for clinicians to determine the inflammation status of patients. Thus, several white blood cells-based indicators had been introduced to play a vital role in the diagnosis and prognosis of kidney disease.[6,21,22] Moreover, A high SIRI represents a high neutrophil and monocyte and a low lymphocyte content. In previous studies, increased neutrophil and monocyte or

decreased lymphocyte counts have been demonstrated to be good predictors for the prognosis of patients with kidney disease. A recent study enrolled 646 peritoneal dialysis patients and demonstrated that after a median 31-month follow-up period, and higher SIRI (1.28) level was significantly associated with increased all-cause mortality and CVD mortality.[13] Similar results had also been found in another study with 369 incident PD patients and they concluded that SIRI was independent indicator for all-cause mortality in PD patients and could provide comparable predictive value and assist clinicians to ameliorate PD management.[23] Alike with this, in the current study, we collected 153 diabetic MHD patients and concluded that a higher SIRI (2.5) level was significantly associated with elevated all-cause mortality. However, the exact mechanism of the SIRI that affects all-cause mortality in diabetes MHD patients is unclear. We believe that except for inflammation, these might at least also explain by malnutrition. A significant negative correlation between SIRI and nutritive indexes (serum albumin, triglyceride, and total cholesterol) was found in this study and it is well-acknowledged that malnutrition had prognostic values for patients with ESKD.[24,25]

Given that the readily accessible for the nomogram, which may be more easy-to-use for physicians to decide the diagnosis or the prognosis of a specific patient, we developed a predictive nomogram that combines the SIRI value and other clinical factors selected by LASSO regression to make the prediction accurate, and then, doctors could early identify diabetic MHD patients at high risk of death along with a timely and effective clinical intervention to improve the prognosis of these patients. And unsurprisingly, in the present investigation, our predictive nomogram displayed high predictive value and was clinically useful for diabetic MHD patients.

However, there were also some limitations in this retrospective study. Firstly, this retrospective analysis was a single-center study with limited samples, which might have potential bias. Secondly, only the initial SIRI value at the first three months of HD therapy was included in this study and we did not analyze changes of them throughout their MHD therapy. Thirdly, there were some important inflammatory markers, such as interleukin, and tumor necrosis factor were missed in this study. Finally, the predictive nomogram did not validate in independent cohorts, and further prospective multicenter studies are needed to corroborate our findings.

Conclusions

In the present study, we first concluded that the initial SIRI, which is simple access and cost-effective parameter, could act as a credible predictor for diabetic MHD patients. Moreover, the suggested nomogram based on the SIRI serves as an effective means for recognizing patients at high risk of death for diabetic MHD patients and could offer a therapeutic cue for patients suffering from particularly inflamed DKD.

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Disclosure

The authors declared that there is no conflict of interest.

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