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Risk factors and preventive measures for abnormal blood pressure during hemodialysis filtration for patients with sepsis

Faktori rizika i mere prevencije poremećaja krvnog pritiska tokom hemodijafiltracije kod bolesnika sa sepsom

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Abstract

Background/Aim. Hemodialysis filtration (HDF) plays an extremely important role in treating patients with sepsis and subsequent acute renal failure. However, abnormal blood pressure (ABP) during HDF badly influences the prognosis and increases all-cause mortality in patients with sepsis. The aim of the study was to investigate risk factors and preventive measures of ABP during HDF for patients with sepsis. **Methods.** A total of 145 patients with sepsis undergoing HDF were included in this study, and they were divided into two groups: the normal blood pressure (NBP) group (n = 89) and the ABP group (n = 56). Their clinical data were collected, and the independent influencing factors for ABP during HDF were assessed by univariate and multivariate logistic regression analyses. A nomogram model for prediction was constructed based on the results of multivariate analysis, and its discrimination and consistency were assessed using receiver operating characteristic and calibration curves. The Kaplan-Meier method was used to plot the survival curve to evaluate the prognosis 28 days after HDF. **Results.** Multivariate logistic regression analysis revealed that age, blood calcium, fasting plasma glucose, intact parathyroid hormone, ultrafiltration volume, and ultrafiltration rate were independent risk factors, whereas albumin was a protective factor for ABP during HDF ($p < 0.05$). The nomogram model exhibited a good fitting effect, with high discrimination and accuracy. Kaplan-Meier survival analysis showed that the NBP group had a significantly higher 28-day survival rate than that of ABP (88.76% vs. 73.21%) ($p < 0.05$). **Conclusion.** The constructed risk model is suitable for identifying high-risk groups and provides a reference for effective prevention and treatment, to lower the incidence rate of ABP and improve the prognosis.

Key words:
acute kidney injury; blood pressure; blood pressure determination; dialysis; prognosis; risk factors; sepsis.

Apstrakt

Uvod/Cilj. Hemodijafiltracija (HDF) ima izuzetno važnu ulogu u lečenju bolesnika sa sepsom i posledičnom akutnom bubrežnom slabošću. Međutim, poremećaj krvnog pritiska (PKP) tokom HDF loše utiče na prognozu i povećava smrtnost od svih uzroka kod bolesnika sa sepsom. Cilj rada bio je da se ispitaju faktori rizika i mere prevencije PKP tokom HDF kod bolesnika sa sepsom. **Metode.** U ovu studiju je ukupno bilo uključeno 145 bolesnika sa sepsom koji su bili podvrgnuti HDF, i bili su podeljeni u dve grupe: grupu sa normalnim krvnim pritiskom (NKP) (n = 89) i grupu sa PKP (n = 56). Prikupljeni su njihovi klinički podaci, a nezavisni faktori uticaja na PKP tokom HDF procenjeni su univarijantnom i multivarijantnom logističkom regresionom analizom. Na osnovu rezultata multivarijantne analize konstruisan je model nomograma za predviđanje i njegova diskriminacija i konzistencija bile su procenjene korišćenjem *receiver operating characteristic* i *cacalibration* krive. Da bi se procenila prognoza 28 dana posle HDF, za crtanje krive preživljavanja korišćen je Kaplan-Majerov metod. **Rezultati.** Multivarijantnom logističkom regresionom analizom otkriveno je da su životno doba, kalcijum u krvi, glukoza u plazmi natašte, intaktni paratireoidni hormon, volumen ultrafiltracije i brzina ultrafiltracije bili nezavisni faktori rizika, dok je albumin bio faktor protekcije od PKP tokom HDF ($p < 0,05$). Model nomograma pokazao je dobar efekat uklapanja, sa visokom diskriminacijom i tačnošću. Kaplan-Majerova analiza preživljavanja pokazala je da je grupa sa NKP imala statistički značajno višu 28-dnevnu stopu preživljavanja u odnosu na grupu sa PKP (88,76% vs. 73,21%) ($p < 0,05$).

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Zaključak. Konstruisani model rizika je pogodan za identifikaciju visokorizičnih grupa i pruža preporuku za efikasnu prevenciju i lečenje, u cilju snižavanja stope incidencije PKP i poboljšanja prognoze.

Ključne reči:
bubreg, akutna insuficijencija; krvni pritisak; krvni pritisak, merenje; hemodijaliza; prognoza; faktori rizika; sepsa.

Introduction

Sepsis is an infection-induced systemic inflammatory response syndrome in humans. Its pathogenesis is that the overloaded inflammatory mediators in the body trigger responses to infections, which often damage multiple organs or tissues, thus easily resulting in the death of patients [1, 2]. Kidney injury, a common complication of sepsis in patients, can give rise to a plunge in the renal function of patients within a short time, which deteriorates the disease, greatly shortens the lifespan, and leads to poor prognosis of the patients [3]. Hemodialysis filtration (HDF) is an effective treatment method with high safety and reliability, which can sustain the life of patients with sepsis and relieve their disease [4]. The action mechanism is that HDF removes harmful substances from blood through extracorporeal blood circulation, regulates the patients' immune function, and provides solutions to high catabolism and capacity overload, thus extending life and improving patients' quality of life [5]. As one of the common complications during HDF, abnormal blood pressure (BP) – ABP is a vital factor influencing the therapeutic effect of HDF [6]. It has been pointed out that ABP triggers physical pain and pain-related fear [7], and even leads to mesenteric ischemia and thrombosis in severe cases. Clarifying factors influencing ABP in the HDF process is conducive to early prevention and treatment, thus decreasing the incidence rate of ABP and increasing the survival rate of patients with sepsis.

The aim of this study was to investigate the risk factors and corresponding preventive measures of ABP during HDF for patients with sepsis. This study was expected to provide clinical evidence for treating sepsis in patients clinically.

Methods

General data

This study was approved by the Ethics Committee of the Taizhou People's Hospital, China (from June 4, 2019). and performed according to the Declaration of Helsinki. Written informed consent was obtained from all subjects. For this retrospective nested case-control study, 145 patients with sepsis undergoing HDF in our Hospital from June 2019 to December 2021 were selected, including 78 males and 67 females, aged 21–68 years (with an average age of 61.47 ± 10.89 years). The clinical course of sepsis in these patients was 3–8 months, with an average of 5.27 ± 1.34 months. The flow chart of subject selection is shown in Figure 1.

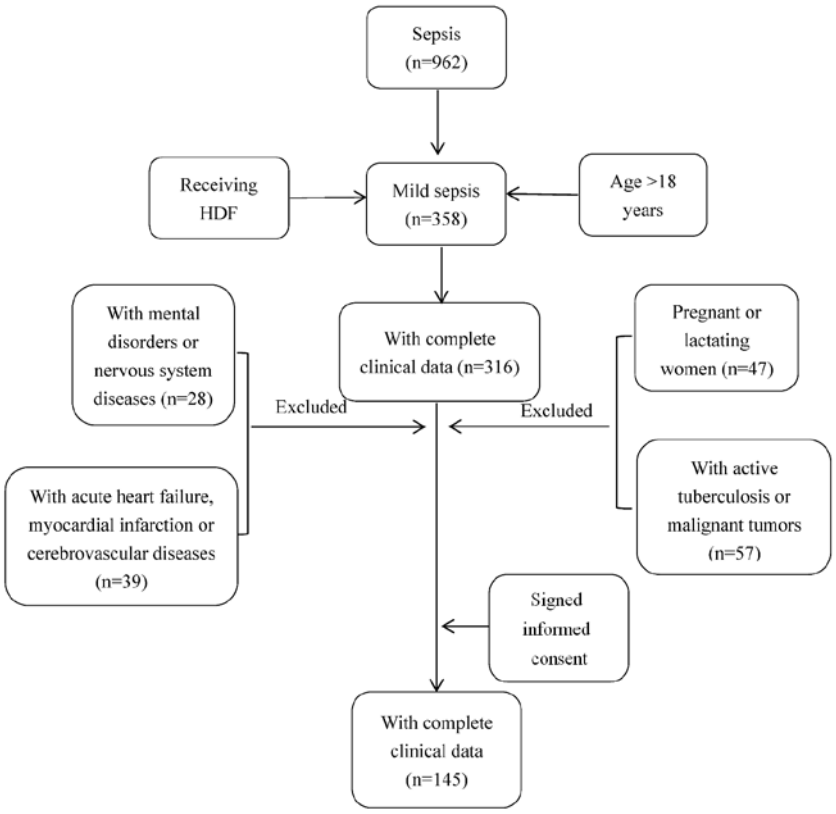

Fig. 1 – Flow chart of subject selection.
HDF – hemodialysis filtration.

Inclusion and exclusion criteria

Inclusion criteria involved: patients over 18 years of age; those meeting the diagnostic criteria for mild sepsis specified in the International Guidelines for the Management of Sepsis and Septic Shock [8]; those receiving HDF; those who received glucocorticoid therapy during dialysis; those with complete clinical data.

Exclusion criteria were set as follows: pregnant or lactating women; patients with active tuberculosis or malignant tumors; those with mental disorders or nervous system diseases; those complicated with acute heart failure, myocardial infarction, or cerebrovascular diseases; those with incomplete clinical data.

Hemodialysis filtration methods

HDF of all patients was performed using Fresenius 4008B hemodialysis machine (Germany) and polysulfone dialysis membranes using the post-dilution method. Blood flow was 200–300 mL/min. HDF was conducted twice to three times a week, 3–4 hrs each time. The dialysate flow was 500 mL/min, the filtration coefficient was 5.5 mL/(h × mmHg), and the surface area of the dialysis membrane was 1.4 m^2.

Blood pressure measurement methods

Invasive BP testing was conducted using the radial artery and *unit* artery as puncture sites. Allen's test was performed before the radial artery puncture; the artery was punctured strictly aseptically and fixed properly. The entire measurement device (BSX-516, Changsha Sinocare Inc., China) included a pressure measurement tube, three-way cannula, pressure sensor, extension tube, heparin saline (1,250 units of heparin sodium in 500 mL of water), and a pressurized bag. During the connection of the arterial indwelling needle, the whole set of tubing was filled with heparin saline, without air leakage or bubbles. After the monitor was connected, the sensor was subjected to zero calibration. After successful calibration, invasive BP monitoring was carried out. Daytime BP (8:00–20:00) and nighttime BP (20:00–8:00) were recorded every 30 min. The effective BP readings throughout the day should be > 80%. The daytime and nighttime BP waveforms and values within 24 hrs were observed.

Diagnostic criteria for abnormal blood pressure

All patients were divided into normal BP (NBP) and ABP groups according to whether they had BP abnormality during HDF. BP abnormality included hypertension and hypotension. The patients were diagnosed with hypotension if the decrease of systolic BP was ≥ 20 mmHg (or if the decrease of the mean arterial pressure was ≥ 10 mmHg) during HDF [9]. The patients were diagnosed with hypertension if the BP rose sharply during HDF or immediately after HDF, and the average arterial pressure increased by at least 15 mmHg [10].

Observational indices

Through literature review of the possible influencing factors for ABP, the clinical data of patients were collected, including 1) basic data: age, gender, body mass index (BMI), complications (hypertension, diabetes mellitus, cerebrovascular and cardiovascular diseases), and primary diseases (diabetic nephropathy, chronic glomerulonephritis, hypertensive renal damage, etc.); 2) blood laboratory indices before HDF: hemoglobin (Hb), albumin, phosphorus, calcium, sodium, total cholesterol (TC), creatinine (Cr), blood urea nitrogen (BUN), fasting plasma glucose (FPG), low-density lipoprotein cholesterol (L-DLC), high-density lipoprotein cholesterol (H-DLC), and intact parathyroid hormone (iPTH); 3) HDF-related data: ultrafiltration volume (UV), ultrafiltration rate (UR), and blood flow; 4) the survival of patients 28 days after HDF observed during the short-term follow-up.

Statistical analysis

Statistical analysis was conducted using SPSS software version 22.0. The normality test was carried out for continuous variables. The measurement data were expressed as mean ± standard deviation, and the count data were represented as numbers (percentages). Intergroup comparison of measurement data conforming to normal distribution was performed by the independent samples *t*-test, and the comparison of count data was conducted with the χ^2 test. With the occurrence of ABP as the dependent variable (Yes = 1, No = 0) and the influencing factors for ABP during HDF in patients with sepsis as the independent variable, stepwise multivariate logistic regression (MLR) analysis was conducted. The values were assigned according to the description in Table 1 (values were assigned to continuous variables after they were converted into binary variables, and then binary variables were converted into numerical variables). A nomogram model for risk prediction was constructed based on the obtained risk factors. The discrimination of the model was examined by plotting the receiver operating characteristic (ROC) curve, and its consistency was evaluated using the

Table 1

Value assignment in multivariate logistic regression analysis

Variable	Values	
	1	0
Dependent		
blood pressure	abnormal	normal
Independent		
gender	female	male
age, years	> 60	> 60
Hemoglobin, g/L	> 110	≤ 60
Albumin, g/L	< 28	≥ 28
Calcium, mmol/L	> 2.30	≤ 2.30
FPG, mmol/L	> 7.9	≤ 7.9
iPTH, pg/mL	> 400	≤ 400
Ultrafiltration volume, mL	> 2,200	≤ 2,200
Ultrafiltration rate, mL/min	> 10	≤ 10

For abbreviations, see Figure 2.

calibration curve. The Kaplan-Meier method was utilized to plot survival curves. The value of $p < 0.05$ represented a statistically significant difference.

Results

Among 145 patients with sepsis, 56 patients were in the ABP (with ABP) and 89 in the NBP group (with no related symptoms). According to the results of univariate analysis of clinical data of patients in the two groups, statistically significant differences were detected concerning gender, age, Hb, albumin, blood calcium, FPG, iPTH, UV, and UR between the two groups of patients ($p < 0.05$). However, no statistically significant differences were observed concerning BMI, complications, primary diseases, TC, Cr, BUN, L-DLC, and H-DLC between the two groups of patients ($p > 0.05$) (Table 2).

MLR analysis revealed that age, blood calcium, FPG, iPTH, UV, and UR were independent risk factors, whereas albumin was a protective factor against ABP during HDF in patients with sepsis ($p < 0.05$) (Table 3).

Table 2

Univariate logistic regression analysis results of clinical data

Variable	ABP group (n = 56)	NBP group (n = 89)	*t*-value/χ^2 value	*p*-value
Male, n (%)	24 (42.86)	54 (60.67)	4.390	0.036
Age, years	63.91 ± 11.32	59.93 ± 10.32	2.068	0.040
BMI, kg/m^2	24.66 ± 4.89	25.57 ± 4.28	1.179	0.240
Complication, n (%)				
hypertension	16 (28.57)	18 (20.22)	1.334	0.248
diabetes mellitus	15 (26.79)	13 (14.61)	3.272	0.070
cerebrovascular disease	15 (26.79)	17 (19.10)	1.180	0.277
cardiovascular disease	16 (28.57)	21 (23.60)	0.448	0.503
Primary disease, n (%)				
diabetic nephropathy	13 (23.21)	16 (17.98)	0.589	0.443
chronic glomerulonephritis	11 (19.64)	13 (14.61)	0.631	0.427
hypertensive renal injury	5 (8.93)	9 (10.11)	0.055	0.814
other	4 (7.14)	12 (13.48)	1.408	0.235
Hemoglobin, g/L	108.76 ± 10.65	115.31 ± 10.94	3.546	< 0.001
Albumin, g/L	27.25 ± 4.94	29.55 ± 5.17	2.653	0.009
Phosphorus, mmol/L	1.81 ± 0.56	1.91 ± 0.59	1.013	0.313
Calcium, mmol/L	2.34 ± 0.15	2.25 ± 0.26	2.354	0.020
Sodium, mmol/L	136.74 ± 2.89	137.42 ± 2.61	1.465	0.145
Total cholesterol, mmol/L	4.56 ± 1.31	4.39 ± 1.02	0.874	0.384
Serum creatinine, μmol/L	663.82 ± 79.54	652.73 ± 81.49	0.805	0.422
BUN, mmol/L	19.22 ± 6.15	17.65 ± 4.93	1.695	0.092
FPG, mmol/L	9.32 ± 1.59	6.92 ± 1.42	9.458	< 0.001
L-DLC, mmol/L	2.87 ± 0.63	2.76 ± 0.55	1.108	0.270
H-DLC, mmol/L	1.25 ± 0.32	1.14 ± 0.43	1.648	0.102
iPTH, pg/mL	470.33 ± 152.42	365.26 ± 120.17	4.614	< 0.001
Ultrafiltration volume, mL	2769.48 ± 429.48	2019.65 ± 478.13	9.556	< 0.001
Ultrafiltration rate, mL/min	9.85 ± 2.98	8.56 ± 2.71	2.685	0.008
Blood flow, mL/min	235.47 ± 24.33	241.29 ± 24.75	1.388	0.167
Type of vascular access			0.342	0.559
autologous arteriovenous fistula	50 (89.29)	82 (92.13)		
tunnel-cuffed catheter	6 (10.71)	7 (7.87)		

ABP – abnormal blood pressure; NBP – normal blood pressure; BMI – body mass index; BUN – blood urea nitrogen; FPG – fasting plasma glucose; L-DLC – low-density cholesterol; H-DLC – high-density cholesterol; iPTH – intact parathyroid hormone.
All values are given as numbers (percentages) or mean ± standard deviation.

Table 3

Multivariate logistic regression analysis results of abnormal blood pressure during hemodialysis filtration

Item	OR	95% CI	*p*-value
Gender	2.353	1.044~3.259	0.069
Age	1.096	1.008~1.935	0.005
Hemoglobin	1.854	1.192~2.048	0.057
Albumin	0.691	0.142~0.973	0.012
Calcium	2.814	2.101~4.075	0.010
FPG	2.208	1.340~3.858	0.004
iPTH	2.762	1.549~4.511	0.011
Ultrafiltration volume	1.824	1.029~3.133	0.024
Ultrafiltration rate	3.415	1.483~5.348	0.003

OR – odds ratio; CI – confidence interval.
For other abbreviations, see Figure 2.

The risk nomogram prediction model of ABP during HDF in patients with sepsis was constructed based on the results of MLR analysis (Figure 2). The results revealed that the risk of ABP rose with the increase of age, blood calcium, FPG, iPTH, UV, and UR, but patients with a higher albumin level before HDF had a relatively small risk of ABP.

The discrimination of the nomogram model was evaluated *via* the ROC curve, and the results showed that the area under the curve (AUC) was 0.877 [95% confidence interval (CI): 0.817–0.956]. The maximum likelihood index of the ROC curve was 0.646, with the corresponding sensitivity and specificity of 79.5% and 85.1%, respectively (Figure 3A). The internal validation of the model by the Bootstrapping method (1,000 samples) illustrated that the C-index of the risk prediction model was 0.865, which represented that the nomogram model had a high overall discrimination (Figure 3B).

The calibration curve of the prediction model was plotted. It was found that the model probability curve in predicting ABP during HDF in patients with sepsis had a good fit with the reference probability curve. In addition, there was no statistically significant difference in the Hosmer-Lemeshow test results ($p > 0.05$), and the prediction index of the model was 0.873, representing the high accuracy of the model (Figure 4).

This study's follow-up rate was 100% (145/145), with no lost cases of patients with sepsis. The 28-day survival of the two groups was recorded, and the survival curves of the two groups of patients were plotted using the Kaplan-Meier method. The results manifested that the 28-day survival rate in the ABP group [73.21% (41/56)] was significantly lower than that in the NBP group [88.76% (79/89)] ($p < 0.05$) (Figure 5).

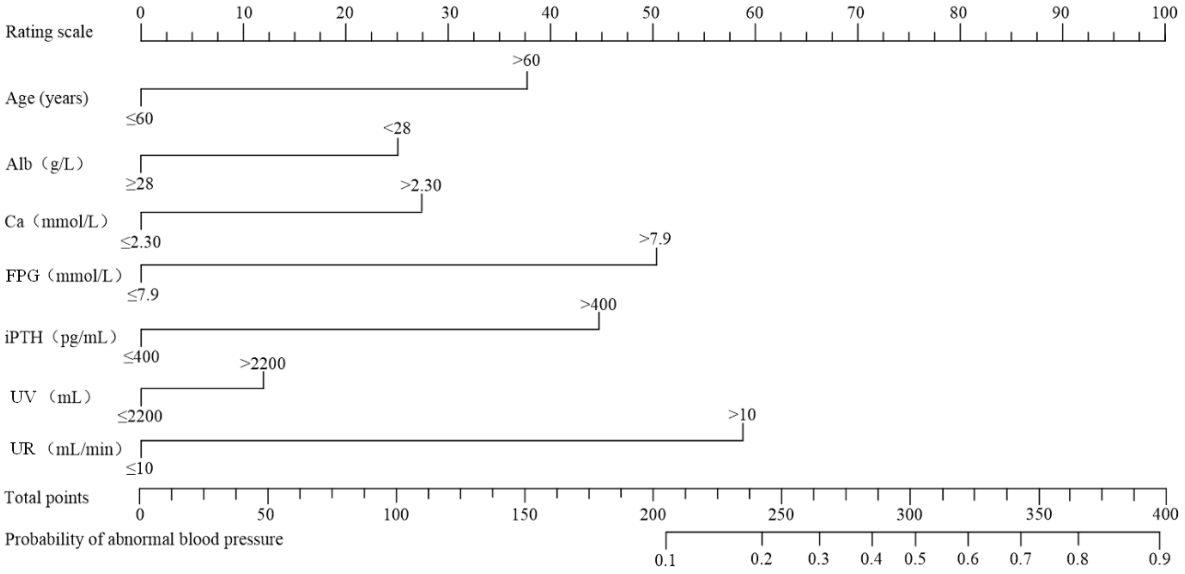

Fig. 2 – Nomogram model for risk prediction of abnormal blood pressure during hemodialysis filtration.
Alb – albumin; Ca – calcium; FPG – fasting plasma glucose; iPTH – intact parathyroid hormone; UV – ultrafiltration volume; UR – ultrafiltration rate.

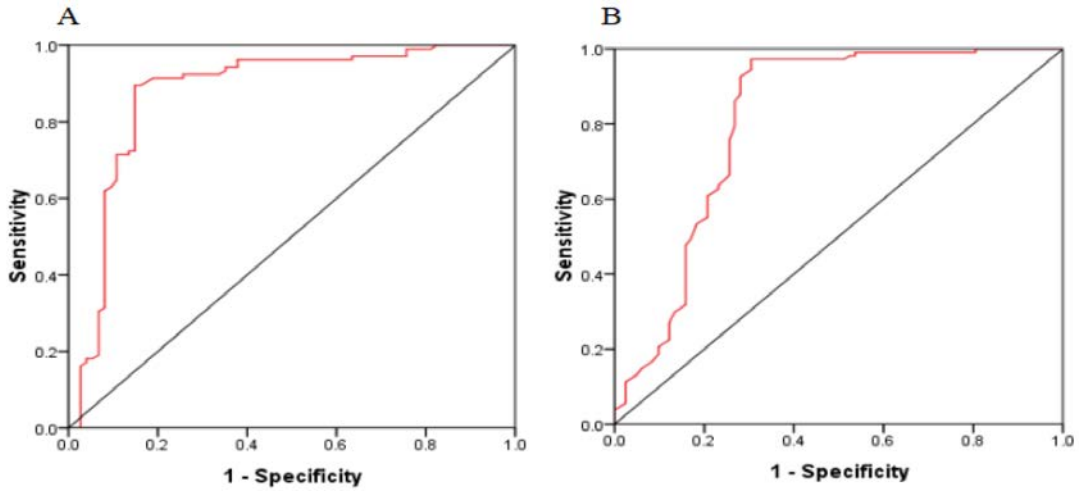

Fig. 3 – Receiver operating characteristic (ROC) curve of the nomogram prediction model.
A) Before internal calibration; B) after internal correction.

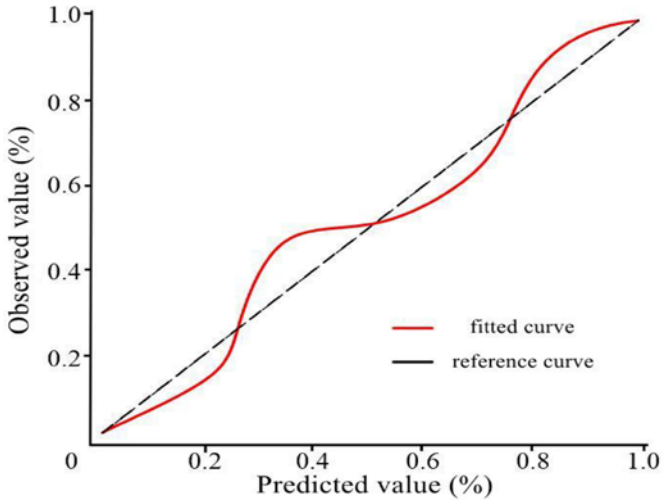

Fig. 4 – Calibration curve of nomogram model for prediction.

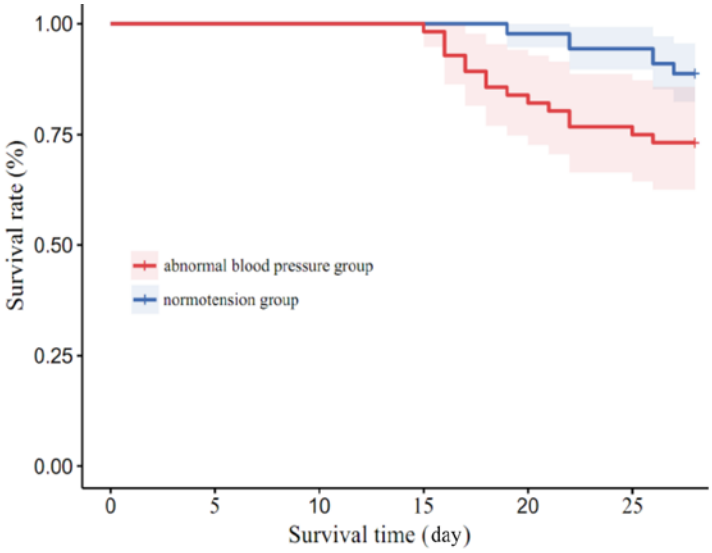

Fig. 5 – Survival curve analysis results.

Discussion

Sepsis is an infection-induced systemic response syndrome featured with high morbidity and mortality rates. Failure to take timely and accurate intervention measures causes organ dysfunction and circulatory disturbance, accompanied by multiple complications, finally leading to aggravation [11, 12]. Hemodialysis, an effective treatment for patients with sepsis, can clear inflammatory cytokines in the body, improve renal function, and prolong the life of patients. It can also adjust the electrolyte balance and acid-base state of the body, so it has been widely used in clinical practice [13]. ABP during HDF in patients is a common complication, which makes the patients more uncomfortable, affects the smooth progress of HDF, and induces other diseases by influencing the adequacy of HDF, thus interfering with the prognosis of patients [14]. ABP during HDF is an independent risk factor for patients' mortality, which remarkably affects the survival rate of patients [15]. Early appropriate measures to interfere with ABP among high-risk patients with sepsis can effectively decrease the incidence rate of ABP and elevate the survival rate of patients with sepsis. In the present study, therefore, the independent influencing factors for ABP during HDF in patients with sepsis were explored to provide a theoretical reference for increasing the survival rate of patients.

Various factors can lead to ABP during HDF in patients. Patients with ABP are older than those with NBP, reflecting that age is a crucial factor affecting BP during HDF [16, 17]. This is consistent with the results of this study which imply that higher age is an independent risk factor for ABP during HDF. The analysis of this study manifested that BP was associated with the function and metabolism of elderly patients. As the patients grow older, the fragility of blood vessels rises. Therefore, hypertension and cardiovascular and cerebrovascular diseases are prone to coincide. This leads to a poor ability to regulate sharp variations in blood volume and increases the probability of ABP during HDF. Albumin is associated with the human body's ability to respond to stress. The stress response declines with decreasing

albumin level, which reduces the effective circulating blood volume and HDF tolerance, thereby increasing the probability of ABP [18]. Blood calcium, a vital index for maintaining body circulation, affects the secretion of anti-inflammatory cytokines by mediating the exocytosis of macrophages. The upregulated calcium^{2+} concentration triggers the occurrence of atherosclerosis and influences the occurrence and development of plaques [19]. Atherosclerosis is an independent influencing factor for cardiovascular disease and death in patients [20], so there is a correlation between a high level of blood calcium and ABP during HDF in patients. This speculation is validated by observation in this study that the blood calcium level of patients with ABP before HDF was remarkably higher than that of patients with NBP, so the blood calcium before HDF was regarded as an independent influencing factor for ABP. Roszkowska-Blaim et al. [21] reported that the probability of hypotension was higher in patients undergoing HDF with a higher FPG level, so the process of HDF and the curative effect on patients were affected. Presumably, the patients with kidney injury and a higher FPG level have a wider variation range of autonomic nerve and vascular diseases, which weakens vascular adaptability during HDF and increases the probability of ABP. With the main function of regulating the blood calcium level, iPTH exerts a significant vasodilating effect. It is able to suppress the effects of multiple hormones such as angiotensin and impede smooth muscle contraction, thereby inducing ABP in patients [22].

The results of this study revealed that the UV and UR of patients in the ABP group were significantly higher than those in the NBP group. The reason is that a larger UV and a higher UR represent a larger liquid clearance volume in the HDF process, leading to a higher tendency to an exceeding level of capillary refilling, reducing the effective circulation volume and increasing the possibility of hypotension. Volume overload between dialysis sessions can aggravate pre-existing hypertension and negatively affect cardiovascular health. This often leads to a higher UR to manage the excess fluid, which can induce adverse outcomes such as abnormal ventricular remodeling and heart failure [23]. Therefore, UV and UR are independent indicators for predicting ABP during HDF in patients with sepsis, and effective control of UV and UR can reduce the incidence rate of ABP.

Based on the above multivariate analysis results, a nomogram model for risk prediction was established, and the discrimination and accuracy of the prediction model were assessed using the ROC and calibration curve. It was found that the constructed prediction model could accurately predict the risk of ABP during HDF in patients with sepsis, which provides a reference for the clinical screening of high-risk septic patients with ABP during HDF. Moreover, the death of patients 28 days after HDF was taken as the endpoint event, and the survival curves of the two groups of patients were drawn and compared in this study. It was discovered that a significant difference in the survival curve was found between the two groups of patients, indicating that ABP during HDF greatly influences the prognosis of patients with sepsis.

In light of the above analysis results of influencing factors for ABP in patients with sepsis, the corresponding nursing measures were proposed to reduce ABP during HDF. Specifically, before HDF, emphasis should be on clinical indices such as age, albumin, blood calcium, FPG, and iPTH of patients with sepsis, especially those with a higher risk of ABP. Besides, exact handovers and records should be guaranteed. Additionally, according to the patient's condition, a reasonable dialysis scheme should be formulated with strict control of the UV and UR. If necessary, drug therapy should be combined or HDF terminated to prevent adverse outcomes.

Limitations of the study

The study had several limitations. First, the research subjects were selected from a single center, with a small sample size. Second, the predictive score in this study was established through retrospective nested case-control analysis of limited clinical data, which was not further verified in a prospective cohort. Third, ABP in patients was only predicted with the presence of abnormality as the dependent variable of the model. In further study, the model can be optimized by considering the occurrence of hypotension or hypertension. Moreover, prospective, multi-center research with enlarged sample sizes can be conducted in the future.

Conclusion

In summary, elderly septic patients with higher levels of blood calcium, fasting plasma glucose, intact parathyroid hormone, ultrafiltration volume, and ultrafiltration rate are prone to abnormal blood pressure during hemodialysis filtration. In contrast, those with a higher albumin level before hemodialysis filtration have a relatively low risk. The constructed risk model is suitable for identifying high-risk groups and provides a reference for reasonable and effective prevention and treatment measures by clinicians to decrease the incidence rate of abnormal blood pressure and improve the prognosis of the patients.

Conflict of interest

The authors declare no conflict of interest.

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