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Original Article

Risk factors for cardiovascular and cerebrovascular events in patients with uremia and hypertension during maintenance hemodialysis

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Abstract: Objectives: This study aimed to investigate risk factors for major adverse cardiovascular and cerebrovascular events (MACCEs) in patients with uremia and hypertension during maintenance hemodialysis (MHD). Methods: Clinical data of patients with uremia and refractory hypertension admitted to Changzhou Fourth People's Hospital (Changzhou Tumor Hospital) from February 2018 to February 2022 were retrospectively collected and analyzed. All patients were treated with MHD and categorized into an MACCE group and a non-MACCE group according to whether MACCEs occurred during the treatment cycle. Univariate analysis and multivariate logistic regression analysis were applied to identify the risk factors for MACCEs in the patients during the treatment period. Results: (1) A total of 156 patients were included in this study, among whom 75 patients were in the MACCE group and 81 in the non-MACCE group, with an MACCE incidence of 48.08%. (2) Diabetes, body mass growth rate, triglyceride (TG), N-terminal pro-brain natriuretic peptide (NT-proBNP), as well as the standard deviation (SD) and coefficient of variability (CV) for both systolic (SBP) and diastolic blood pressure (DBP) showed significant differences between the two groups, with $P<0.05$. (3) Diabetes, body mass growth rate ≥5.54%, TG≥1.40 mmol/L, NT-proBNP≥5.82 ng/L, SBP-SD≥13.52, SBP-CV≥8.63, DBP-SD≥8.14, and DBP-CV≥8.82 were found to be risk factors for MACCEs in the patients. Conclusions: The incidence of MACCEs in patients with uremia and hypertension during MHD was associated with diabetes, body mass growth rate, TG, NT-proBNP, SBP-SD, SBP-CV, DBP-SD, and DBP-CV.Early screening for high-risk patients and positive intervention measures should be given to reduce the risk of MACCEs to enhance the safety of dialysis procedures.

Keywords: Uremia, hypertension, maintenance hemodialysis, cardiovascular and cerebrovascular events, risk factors

Introduction

Uremia, indicating the uremic stage of chronic kidney diseases (CKDs), is an advanced stage of chronic renal failure and other kidney diseases [1]. Hemodialysis serves as a renal replacement therapy that facilitates body metabolism by eliminating metabolic waste and maintaining homeostasis of water, electrolytes, and acid-base balance, thereby stabilizing the internal environment and extending patient survival. Hemodialysis is currently a widely used and effective treatment method for uremia [2]. Ongoing advancements in blood purification technologies have significantly improved the survival rate of uremia patients [3], but in the maintenance hemodialysis (MHD), it is common for patients to experience hypertension, especially fluctuation in blood pressure, which increases the incidence and mortality of major adverse cardiovascular and cerebrovascular events (MACCEs) [4]. Relevant research findings showed that cardiovascular and cerebrovascular events were major risk factors for death in patients undergoing MHD, with a mortality of 36% and 11%, respectively [5]. In the treatment cycle of MHD, there are many factors causing MACCEs in uremia patients with hypertension, but there is no unified understanding currently. How to reduce the occurrence of MACCEs during MHD is an urgent issue to be addressed. Analysis of risk factors for MACCEs

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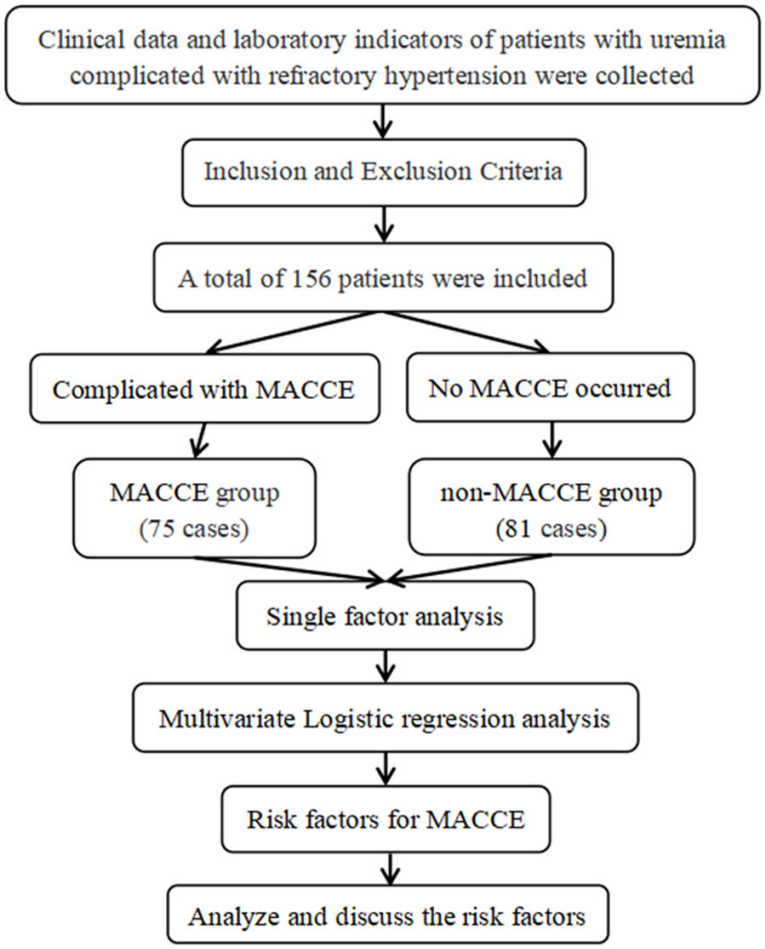

Figure 1. The flow chart of this study. MACCE: major adverse cardiovascular and cerebrovascular event.

in uremia patients with hypertension is of great significance for guiding clinical preventive measures. At present, there are few reports focusing on this population. Therefore, this study retrospectively analyzed the occurrence and risk factors for MACCEs in uremia patients with refractory hypertension treated with MHD from February 2018 to February 2022 in our hospital. The aim was to offer a theoretical basis for the clinical treatment of uremia and guide clinical intervention measures, so as to reduce the occurrence of MACCEs, improve the quality of life of patients, and reduce the fatality rate.

Materials and methods

Patients

The flow chart of this study is shown in **Figure 1**. Clinical data and laboratory indicators of patients with uremia and refractory hypertension admitted to Changzhou Fourth People's Hospital (Changzhou Tumor Hospital) from February 2018 to February 2022 were collected and retrospectively analyzed. Inclusion criteria: (1) patients who met the diagnostic criteria of stage 5 CKDs [6] and hypertension [7] established by the world health organization [7]; (2) patients who had the indications for MHD and received MHD; (3) patients whose hemodialysis time was more than 12 months, and the hemodialysis was performed 3 times a week, 4 hours each time. Exclusion criteria: (1) patients with severe liver diseases or chronic infectious diseases; (2) patients at risk of severe bleeding; (3) patients with mental disorders; (4) patients with low treatment compliance; (5) patients with missing data in clinical information, blood biochemical indices, blood lipid indices, and blood pressure readings. This study was approved by the medical ethics committee of Changzhou Fourth People's Hospital (Changzhou Tumor Hospital).

Procedures of maintenance dialysis

(1) Timing: K/DOQI recommended that when patients with estimated glomerular filtration rate (eGFR) less than 15 (mL/min/1.73 m^2) or weekly urea Kt/V less than 2.0 at stage 5 of CKDs, nephrologists could evaluate the benefits and risks of initiating renal replacement therapy and begin preparation for dialysis. It is generally recommended that non-diabetic patients with eGFR less than 10 (mL/min/1.73 m^2) may start dialysis, while diabetic patients with eGFR less than 15 (mL/min/1.73 m^2) may start dialysis, and some patients with renal failure and special comorbidities may need to start dialysis earlier. (2) Dialysis regimen: Hemodialysis was performed 3 times a week, 4 hours each time. Dialysis blood flow

was 200 mL/min-250 mL/min, and dialysate flow was 500 mL/min. Vascular access was by autologous arteriovenous fistula or long-term jugular vein catheter (Tianjin Jingyi Micro Guide Technology Co., LTD.).

Data collection

Both clinical data and laboratory indicators of patients were collected. (1) General information included gender, diabetes, hyperlipidemia, hyperphosphatemia, smoking history, drinking history, age, course of disease, body mass growth rate, and dialysis age. (2) Main indicators: plasma-albumin, hemoglobin, blood calcium, serum inorganic phosphorus, serum sodium, calcium-phosphorus product, triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), urea, serum creatinine, uric Acid, N-terminal pro-brain natriuretic peptide (NT-proBNP), systolic blood pressure (SBP), diastolic blood pressure (DBP), their standard deviations (SBP-SD, DBP-SD) and coefficient of variability (SBP-CV, DBP-CV), and adiponectin.

Diagnostic criteria and grouping

(1) The diagnostic criteria for hypertension follow the 2010 Guidelines for the Diagnosis and Treatment of Hypertension in China [8]: Systolic blood pressure ≥140 mmHg (1 mmHg = 0.133 kPa) or diastolic blood pressure ≥90 mmHg. (2) Diagnostic criteria for MACCEs [9] are according to K/DOQI guidelines, including myocardial infarction, unstable angina pectoris, coronary artery bypass grafting, percutaneous coronary intervention, heart failure requiring hospitalization, ischemic heart disease, myocardial infarction, and malignant arrhythmia. Cerebrovascular events included cerebral hemorrhagic and ischemic stroke, cerebral infarction, congestive heart failure, and transient cerebral ischemia. (3) Grouping: The incidence of MACCEs was counted. The patients with MACCEs were included in an MACCE group, and the ones without MACCEs were in a non-MACCE group.

Detection methods of relevant indicators

To measure the blood biochemical indices and serum adiponectin, 6 mL fasting blood was extracted in the morning, and 0.3 mL 3.84% citrate was added to the blood samples and centrifuged at 3000 r/min for 10 min. Then, the plasma was separated and stored at -30°C for examination. Blood lipid indices (TG, TC, LDL-C, and HDL-C) were determined by enzyme colorimetry (the kits were from Zhejiang Fukang Biotechnology Co., LTD.). Electrolytes (blood sodium, blood calcium, blood phosphorus), renal function indexes (urea, blood creatinine, uric acid), and serum NT-proBNP were measured by conventional methods. Adiponectin was determined by radioimmunoassay (The kits were from Qingdao Lubo Jianye Environmental Protection Technology Co., LTD.).

Blood pressure variability (BPV): Ambulatory blood pressure monitoring (ABPM) was performed using an arterial blood pressure monitor (IEM company, model: Mobil-O-graph). The blood pressure was measured every 30 minutes from 06:00 to 22:00 in the daytime and every 60 minutes from 22:00 to next 06:00. Referring to the research method of Rothwell et al. [10], the variability of SBP and DBP was determined by calculating the SD and CV. The SD of the mean blood pressure values was calculated from 3 measures, CV = SD/mean blood pressure. According to the European hypertension guidelines, the ABPM hypertension criteria are [11, 12]: 24 h mean blood pressure ≥130/80 mmHg, daytime mean blood pressure ≥135/85 mmHg, night mean blood pressure ≥125/75 mmHg, or night mean systolic blood pressure ≥125 mmHg. Dipper-type blood pressure was defined as nocturnal mean blood pressure that is at least 10% lower than the diurnal mean, while non-dipper-type blood pressure was defined to a reduction in nocturnal blood pressure as decreased blood pressure <10%.

Statistical methods

SPSS 22.0 was used for data analysis. Qualitative data were expressed by [n (%)]. Quantitative data were expressed by ($\overline{x} \pm s$), and processed using t-test. Univariate analysis and multivariate logistic regression model were applied to investigate the related factors for MACCEs in patients with uremia and hypertension during MHD. $P<0.05$ was a statistically significant difference.

Results

Univariate analysis of risk factors for MACCEs

Among the 156 patients included in this study, 75 patients had MACCEs and 81 did not during the MHD, with an incidence of 48.08%.

Table 1. Univariate analysis of risk factors for MACCEs in patients with uremia and hypertension

Influencing factor	MACCE group (n = 75)	Non-MACCE group (n = 81)	t/x^2	*P*
Gender (Female/male)	28/47	29/52	0.039	0.843
Concomitant disease				
Diabetes	24 (32.00)	4 (4.94)	19.365	<0.001
Hyperlipidemia	18 (24.00)	23 (28.40)	0.388	0.533
Hyperphosphatemia	8 (10.67)	7 (8.64)	0.184	0.668
Smoking history	25 (33.33)	29 (35.80)	0.105	0.746
Drinking history	12 (16.00)	9 (11.11)	0.799	0.371
Age (year)	54.22±8.39	53.87±7.16	0.281	0.779
Course of disease (year)	2.58±0.57	2.61±0.42	0.376	0.707
BMI (kg/m^2)	22.53±2.04	22.49±2.13	0.120	0.905
Growth rate of body mass (%)	7.02±1.33	4.86±1.25	10.430	<0.001
Dialysis age (month)	8.43±2.34	8.52±2.16	0.250	0.803
Blood biochemical indexes				
Plasma-albumin (g/L)	38.22±3.39	38.41±3.10	0.366	0.715
Hemoglobin (g/L)	113.25±12.48	112.59±13.32	0.319	0.750
Blood calcium (mmol/L)	2.28±0.22	2.31±0.17	0.957	0.340
Serum inorganic phosphorus (mmol/L)	2.48±0.52	2.42±0.43	0.788	0.432
Serum sodium (mmol/L)	137.28±4.19	136.85±4.25	0.636	0.526
Calcium-phosphorus product ($mmol^2/L^2$)	5.48±0.62	5.39±0.47	1.026	0.306
TG (mmol/L)	1.29±0.42	1.13±0.30	2.753	0.007
TC (mmol/L)	4.42±0.58	4.38±0.29	0.551	0.583
LDL-C (mmol/L)	2.74±0.92	2.66±1.03	0.510	0.611
HDL-C (mmol/L)	1.01±0.11	0.99±0.08	1.306	0.194
Urea (mmol/L)	34.25±6.38	33.74±7.41	0.459	0.647
Serum creatinine (μmol/L)	915.26±25.18	917.02±20.27	0.483	0.630
Uric Acid (μmol/L)	402.55±33.16	405.19±28.87	0.531	0.596
NT-proBNP (ng/L)	6.28±0.47	5.88±0.62	4.514	<0.001
Blood-pressure parameter acquisition				
SBP	143.45±12.28	142.89±11.47	0.295	0.769
DBP	96.21±8.84	95.52±9.13	0.479	0.633
SBP-SD	19.33±4.26	9.25±3.02	17.150	<0.001
SBP-CV	13.17±3.21	5.87±1.85	17.560	<0.001
DBP-SD	10.82±3.29	5.44±1.62	13.100	<0.001
DBP-CV	14.16±4.23	6.24±2.05	15.050	<0.001
Adiponectin	5.37±1.64	5.42±1.38	0.2066	0.837

Note: SD: standard deviation; CV: coefficient of variation; BMI: body mass index; TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

No significant differences were found in the comparisons of gender, hyperlipidemia, hyperphosphatemia, smoking history, drinking history, age, course of the disease, body mass index (BMI), dialysis age, plasma albumin, hemoglobin, blood calcium, blood phosphorus, blood sodium, calcium-phosphorus product, TC, LDL-C, HDL-C, urea, serum creatinine, uric acid, SBP, DBP, or adiponectin between the MACCE group and the non-MACCE group, P>0.05. However, the two groups were significantly different in terms of diabetes, body mass growth rate, TG, NT-proBNP, SBP-SD, SBP-CV, DBP-SD, and DBP-CV, P<0.05. See **Table 1**. Distribution of diabetic cases, body weight growth rate, TG, NT-proBNP, SBP-SD, SBP-CV, DBP-SD, and DBP-CV in the two groups are shown in **Figure 2**.

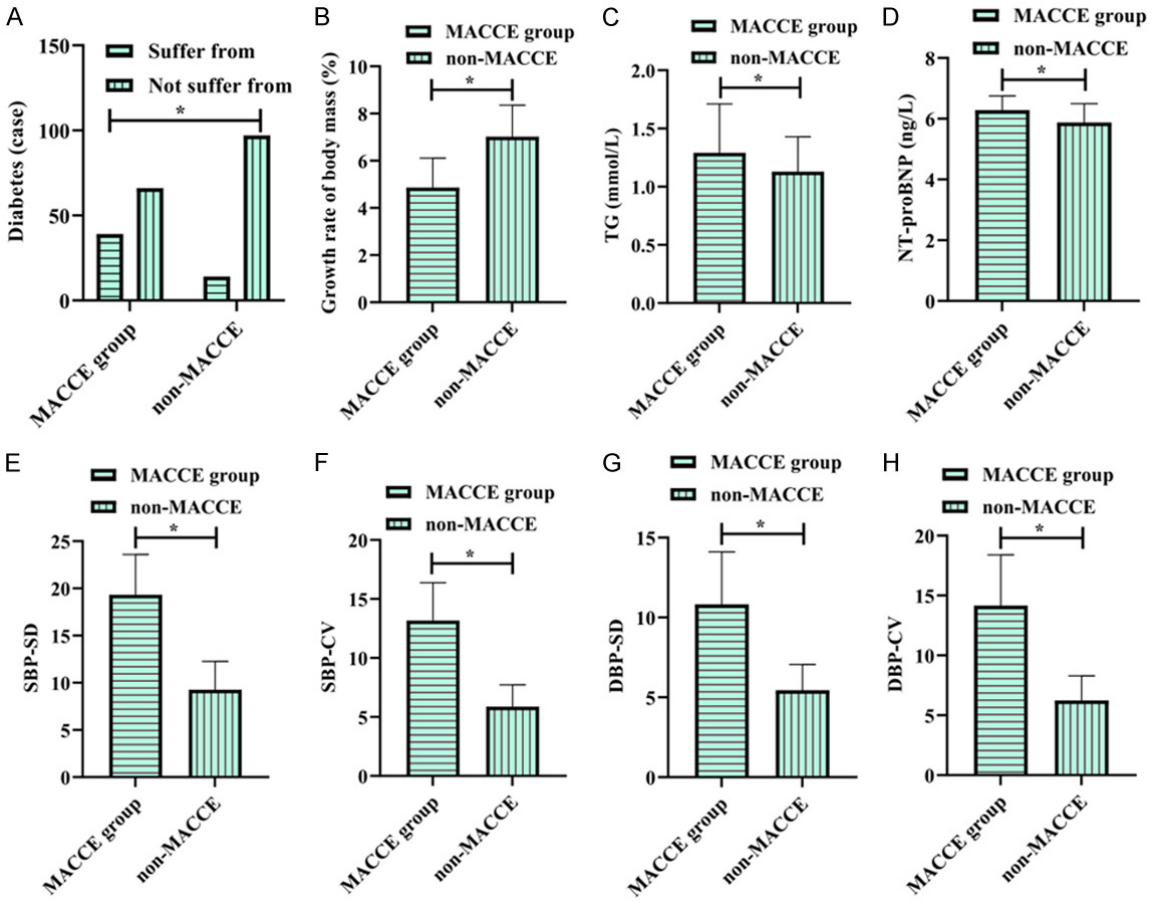

Figure 2. Distribution of diabetic cases and body weight growth rate, TG, NT-proBNP, SBP-SD, SBP-CV, DBP-SD, and DBP-CV in the two groups. A. Diabetes; B. Growth rate of body mass; C. TG; D. NT-proBNP; E. SBP-SD; F. SBP-CV; G. DBP-SD; H. DBP-CV. MACCE: major adverse cardiovascular and cerebrovascular event; TG: triglyceride; NT-proBNP: N-terminal pro-brain natriuretic peptide; SBP-SD: systolic blood pressure-standard deviation; SBP-CV: systolic blood pressure-coefficient of variability; DBP-SD: diastolic blood pressure-standard deviation; DBP-CV: diastolic blood pressure-coefficient of variability.

Multivariate analysis of risk factors for MACCEs

The items with statistical significance in the univariate analysis (diabetes, body mass growth rate, TG, NT-proBNP, SBP-SD, SBP-CV, DBP-SD, and DBP-CV) were taken as independent variables, and the ROC curve was used to find the optimal cut-off value of the continuous variables. The results of ROC curve analysis are shown in **Table 2** and **Figure 3**. Independent variables, optimal cut-off values, and assignment are shown in **Table 3**. Using multivariate logistic regression analysis, diabetes, body mass growth rate ≥5.54%, TG≥1.40 mmol/L, NT-proBNP≥5.82 ng/L, SBP-SD≥13.52, SBP-CV≥8.63, DBP-SD≥8.14, and DBP-CV≥8.82 were found to be significant risk factors for MACCEs in uremia patients with hypertension ($P<0.05$), as shown in **Table 4**.

Discussion

Hypertension in hemodialysis patients is associated with renal failure due to primary hypertension and renovascular hypertension from kidney diseases, along with hemodialysis-related factors [13]. The relationship between blood pressure during dialysis and mortality risk is U-shaped, with both elevated and low post-dialysis SBP levels being associated with a higher risk of cardiovascular death, and the mortality is significantly increased when the DBP is greater than 109 mmHg [14]. MACCEs are important causes of death in uremic patients during MHD [15].

Table 2. Results of ROC curve analysis

Independent variable	Area under the curve	Standard error	P	95% CI	
				Floor limit	Upper limit
Diabetes	0.635	0.045	0.004	0.547	0.723
Growth rate of body mass	0.889	0.028	<0.001	0.835	0.944
TG	0.635	0.046	0.004	0.545	0.724
NT-proBNP	0.694	0.042	<0.001	0.612	0.777
SBP-SD	0.974	0.011	<0.001	0.954	0.995
SBP-CV	0.980	0.008	<0.001	0.964	0.997
DBP-SD	0.928	0.022	<0.001	0.886	0.971
DBP-CV	0.956	0.016	<0.001	0.924	0.987

Note: TG: triglyceride; NT-proBNP: N-terminal pro-brain natriuretic peptide; SBP-SD: systolic blood pressure-standard deviation; SBP-CV: systolic blood pressure-coefficient of variability; DBP-SD: diastolic blood pressure-standard deviation; DBP-CV: diastolic blood pressure-coefficient of variability.

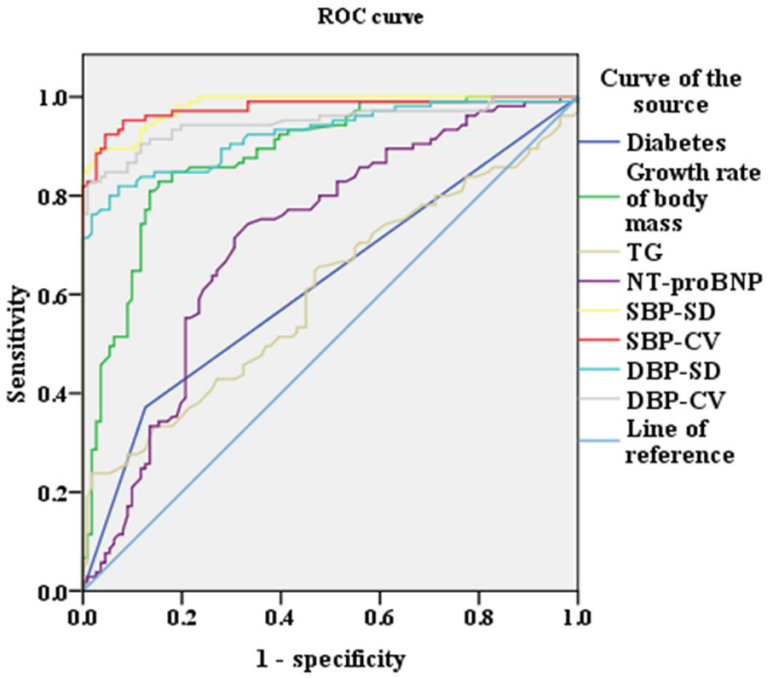

Figure 3. ROC curve. TG: triglyceride; NT-proBNP: N-terminal pro-brain natriuretic peptide; SBP-SD: systolic blood pressure-standard deviation; SBP-CV: systolic blood pressure-coefficient of variability; DBP-SD: diastolic blood pressure-standard deviation; DBP-CV: diastolic blood pressure-coefficient of variability.

In this study, patients with uremia and refractory hypertension were included and the incidence of MACCEs was found to be 48.08%, similar to the results of previous studies [16]. It was identified that diabetes, body mass growth rate ≥5.54%, TG≥1.40 mmol/L, NT-proBNP≥5.82 ng/L, SBP-SD≥13.52, SBP-CV≥8.63, DBP-SD≥8.14, and DBP-CV≥8.82 were risk factors for MACCEs in these patients. Patients with diabetes were more prone to MACCEs [17]. Hypertension can significantly increase the risk of cerebral hemorrhage, and diabetes is also a risk factor for vascular diseases [18, 19]. The concurrent presence of hypertension and diabetes can greatly increase the risk of MACCEs in uremic patients. Furthermore, hypertension is related to BMI and cardiovascular and cerebrovascular diseases [20, 21]. Hypertension contributes to increased body mass in patients, which in turn raises the incidence of MACCEs. This higher BMI is associated with a greater incidence of hypertension, hyperlipidemia, arteriosclerosis, and diabetes, thus causing the development of MACCEs. Consequently, weight gain is implicated in heightened risk of MACCE.

The results of this study showed that the risk of MACCEs was significantly increased when the body mass growth rate exceeded 5.54%. Lipid and complex carbohydrate accumulation, hemorrhage, thrombosis, fibrous hyperplasia, and calcareous deposition are the basis of atherosclerosis [22]. TG is an important part of lipid substances, and an increase in TG leads to augmented lipid accumulation, promoting the onset and progression of atherosclerosis. This condition is characterized by the thickening

Table 3. Risk factors and evaluation of MACCEs in patients with uremia and hypertension

Factor	Code	Assignment
Diabetes	X1	0 = Have, 1 = Not have
Growth rate of body mass	X2	0 = <5.54%, 1 = ≥5.54%
TG	X3	0 = <1.40 mmol/L, 1 = ≥1.40 mmol/L
NT-proBNP	X4	0 = <5.82 ng/L, 1 = ≥5.82 ng/L
SBP-SD	X5	0 = <13.52, 1 = ≥13.52
SBP-CV	X6	0 = <8.63, 1 = ≥8.63
DBP-SD	X7	0 = <8.14, 1 = ≥8.14
DBP-CV	X8	0 = <8.82, 1 = ≥8.82

Note: TG: triglyceride; NT-proBNP: N-terminal pro-brain natriuretic peptide; SBP-SD: systolic blood pressure-standard deviation; SBP-CV: systolic blood pressure-coefficient of variability; DBP-SD: diastolic blood pressure-standard deviation; DBP-CV: diastolic blood pressure-coefficient of variability.

Table 4. Results of multivariate logistic regression analysis

Independent variable	β	Wald χ^2	*P*	OR (95% CI)
Diabetes	3.074	12.458	<0.001	21.633 (3.924-119.263)
Growth rate of body mass	3.202	21.268	<0.001	24.578 (6.303-95.835)
TG	2.188	7.428	0.006	8.917 (1.849-43.007)
NT-proBNP	2.512	13.148	<0.001	12.329 (3.171-47.926)
SBP-SD	2.357	13.149	<0.001	10.560 (2.954-37.756)
SBP-CV	2.431	12.233	<0.001	11.370 (2.912-44.397)
DBP-SD	2.299	11.138	0.001	9.967 (2.583-38.460)
DBP-CV	2.062	10.202	0.001	7.860 (2.218-27.852)

Note: TG: triglyceride; NT-proBNP: N-terminal pro-brain natriuretic peptide; SBP-SD: systolic blood pressure-standard deviation; SBP-CV: systolic blood pressure-coefficient of variability; DBP-SD: diastolic blood pressure-standard deviation; DBP-CV: diastolic blood pressure-coefficient of variability.

and hardening of arterial walls, loss of elasticity, and the formation or rupture of intimal plaque, resulting in stenosis or occlusion of the lumen. Such changes impair arterial blood supply function, precipitating cardiovascular complications and elevating the risk of MACCEs. NT-proBNP is a serum marker mainly synthesized by cardiomyocytes. Excessive ventricular wall tension stimulates cardiomyocytes [23] and release of NT-proBNP, a myocardial marker that reflects cardiac compensatory function. Elevated levels of NT-proBNP in patients suggests reduced cardiac compensation, thereby increasing the likelihood of cardiovascular issues.

The results of this study showed that SBP-SD, SBP-CV, DBP-SD, and DBP-CV were risk factors for MACCEs in patients with uremia and hypertension during MHD, which are consistent with relevant research results [24]. BPV is a clinical indicator reflecting the fluctuation degree of blood pressure over a certain period [25]. Clinical blood pressure SD and CV are commonly used to reflect the level of BPV, which is an important risk factor for target organ damage in patients with hypertension. SBP-SD and DBP-SD are the main indexes reflecting BPV. Recent studies have found that BPV is positively correlated with the occurrence of MACCEs [26]. In addition, the instability of SBP-SD and DBP-SD increased the risk of cardiovascular adverse events [27]. The peripheral blood inflammatory response caused by blood pressure variability and its effect on cardiovascular cell proliferation and apoptosis are the main mechanisms of left ventricular hypertrophy in hypertensive patients. Increased BPV in hypertensive patients can lead to stress response of the body, which stimulates the self-defense system, promotes the expression of inflammatory factors in cardiomyocytes, activates the chronic inflammatory response in the cardiac microenvironment, and further aggravates the inflammatory response. Inflammation can accelerate the process of coronary atheroscle-

rosis and cardiac remodeling, which eventually leads to left ventricular hypertrophy. In addition, BPV can also induce abnormal proliferation, apoptosis, hypertrophy, and proliferation of cardiomyocytes by regulating the renin-angiotensin system and inducing left ventricular hypertrophy [28, 29].

However, this is a single-center retrospective study with a limited number of included cases, which may lead to bias in the results. Therefore, the findings need to be confirmed by multi-center studies with larger number of patients.

The incidence of MACCEs in patients with uremia and hypertension during MHD is related to diabetes, body mass growth rate, TG, NT-proBNP, SBP-SD, SBP-CV, DBP-SD, and DBP-CV. Early screening of high-risk patients and positive intervention measures should be given to reduce the risk of MACCEs and enhance the safety of dialysis procedures.

Disclosure of conflict of interest

None.

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