Effect of Serum Magnesium Level on Arteriovenous Fistula Dysfunction in Patients on Maintenance Hemodialysis

Ann. Ital. Chir., 2025 96, 4: 478–487
https://doi.org/10.62713/aic.3869

Wu-Bin Yao[1,†], Yan Shen[1,†], Liang-Lan Shen[1], Xiao-Hua Wang[2], Hong-Li Yang[1], Jia-Jia Chen[1], Lu-Lu Ma[1], Hua-Xing Huang[1]

[1]Department of Nephrology, The Second Affiliated Hospital of Nantong University, 226001 Nantong, Jiangsu, China
[2]Department of Endocrinology and Metabolism, The Second Affiliated Hospital of Nantong University, 226001 Nantong, Jiangsu, China

AIM: To investigate the effect of magnesium level on the arteriovenous fistula (AVF) dysfunction in patients on maintenance hemodialysis (MHD).

METHODS: We selected patients who underwent AVF surgery at The Second Affiliated Hospital of Nantong University from May 2011 to May 2022 and received MHD regularly for over 3 months. Patients were divided into dysfunction and non-dysfunction groups based on their AVF function, with follow-up until 30 November 2022. Retrospective data collection included pre-dialysis general data and clinical laboratory indicators. The magnesium cut-off for AVF dysfunction prediction was determined using the receiver operating characteristic (ROC) curve, and patients were categorized into high and low magnesium groups. AVF survival rates were compared using Kaplan-Meier methods, and the risk of AVF dysfunction and independent risk factors were analyzed with logistic and Cox regressions.

RESULTS: In a study of 263 hemodialysis patients with a median age of 61 years, including 164 males (62.4%), 95 developed AVF dysfunction over a median follow-up of 32 months. Two groups of MHD patients were classified based on their AVF function: 95 in the dysfunction group and 168 in the non-dysfunction group. The subjects in the dysfunction group were older than those in the non-dysfunction group. Compared with the non-dysfunction group, the dysfunction group suffered significant reduction in magnesium and creatinine levels ($p < 0.05$), and significant increase in calcium and hemoglobin levels ($p < 0.05$). The ROC curve results showed that magnesium = 0.88 mmol/L was the best critical point for predicting AVF dysfunction in MHD patients, with a sensitivity of 68.42% and a specificity of 77.38%. The results of Kaplan–Meier survival analysis showed that the AVF dysfunction in the low magnesium group was significantly higher than that in the high magnesium group (log-rank $\chi^2 = 68.678$, $p < 0.001$). Logistic analysis showed that the low magnesium group was 9.223 times more likely to experience AVF dysfunction than the high magnesium group after adjusting for multiple confounding factors (odds ratio [OR] = 9.223, 95% confidence interval [CI], 4.876–17.445; $p < 0.001$). After adjusting for multiple confounding factors, multivariate Cox regression analysis suggested that advanced age, low serum magnesium, high serum calcium and high hemoglobin were independent risk factors for AVF failure in MHD patients. The risk in the low serum magnesium group was 4.534 times higher than that in the high serum magnesium group (hazard ratio [HR] = 4.534, 95% CI, 2.633–7.808; $p < 0.001$).

CONCLUSIONS: Low serum magnesium is an independent risk factor for AVF dysfunction and can be used as a predictor of AVF dysfunction.

Keywords: maintenance hemodialysis; arteriovenous fistula dysfunction; serum magnesium

Introduction

Maintenance hemodialysis (MHD) is a treatment that uses cardiopulmonary bypass technology to improve azotemia, volume loading, electrolyte disorders, and acid-base abnormalities in end-stage renal disease (ESRD) patients [1]. Arteriovenous fistula (AVF) is the critical vascular access of choice for individuals undergoing long-term hemodialysis, and AVF use reduces complications, improves hemodialysis access survival, and reduces the risk of death compared to arteriovenous graft or central venous catheter use [2,3]. Magnesium is an important cation in the human body and involved in a number of physiological functions in the body, such as maintaining environmental stability, improving bone metabolism, regulating nerve function, affecting cardiac rhythm, among others [4]. Previous studies have shown that hypomagnesemia may be one of the risk factors for the progression of chronic kidney disease (CKD) and is associated with vascular calcification and cardiovascular events in CKD patients [5–7]. Recent studies have highlighted the role of magnesium in vascular health, including its protective effects against vascular calcification and atherosclerosis, which are key factors in AVF dys-

Submitted: 17 November 2024 Revised: 22 January 2025 Accepted: 20 February 2025 Published: 10 April 2025
Correspondence to: Hua-Xing Huang, Department of Nephrology, The Second Affiliated Hospital of Nantong University, 226001 Nantong, Jiangsu, China (e-mail: huasumg@126.com).
† *These authors contributed equally.*

function [8–10]. For instance, a recent CORDIOPREV study by Rodríguez-Ortiz *et al*. [11] demonstrated a significant association between low serum magnesium and carotid atherosclerosis, further supporting the potential impact of magnesium on AVF patency.

Therefore, in this study investigated serum magnesium of patients with ESRD was tested, and analyzed the effects of serum magnesium on AVF dysfunction were analyzed. Given the established importance of the AVF in hemodialysis patients and the potential impact of magnesium on vascular health, understanding the relationship between serum magnesium and AVF dysfunction could offer valuable insights for improving clinical outcomes in ESRD patients undergoing long-term hemodialysis.

Materials and Methods

Patients

The study subjects were selected from patients at The Second Affiliated Hospital of Nantong University, with data collected from May 2011 to May 2022. Inclusion criteria of this study include: (i) patients consistent with the ESRD diagnosis, and aged ≥18 years old; (ii) patients undergoing hemodialysis treatment time ≥3 months; and (iii) patients agreed to participate in the study and signed informed consent. Individuals meeting the following criteria were excluded from this study: (i) patients switching to peritoneal dialysis or combined hemodialysis; (ii) patients with kidney transplantation; (iii) patients with acute kidney injury; (iv) patients with liver disease and malignancy; (v) patients with serious cardiopulmonary complications; and (vi) patients with incomplete clinical data. A total of 324 patients on MHD aged ≥18 years were included in the study. Five cases had undergone hemodialysis for less than three months, one case presented with acute kidney injury, 12 cases underwent a change in transperitoneal dialysis, 18 cases had undergone renal transplantation, three cases had malignant disease, five cases had severe heart failure, and 17 cases were lost to follow-up. Following patient exclusion, 263 patients were selected for this study (Fig. 1).

Data Collection

Retrospective data of a total of 263 ESRD patients who underwent AVF were collected from the medical record management system and hemodialysis system. The data set included general information on age, gender, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), primary disease, complications and smoking history. Additionally, the data set also included pre-dialysis laboratory results, including hemoglobin (Hb), white blood cell (WBC), platelets (PLT), serum creatinine (Scr), uric acid (UA), cystatin C (Cys-C), β2 microglobulin (β2-MG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), apolipoprotein A, apolipoprotein B, hypersensitive C-reactive protein (hsCRP), thyroid stimulating hormone (TSH), blood glucose (Glu), lactate dehydrogenase (LDH), alpha-hydroxybutyrate dehydrogenase (HBDH), serum potassium (K), serum phosphorus (P), serum calcium (Ca), serum magnesium (Mg) and albumin (ALB).

Definitions and Formulas

BMI was calculated with height and weight: BMI = weight (kg)/height^2 (m^2). All patients were treated on dialysis using the standard 1.5 m^2 diameter polysulfone membrane dialyzer (model AK 96; Gambro, Lund, Sweden). The dialysate contained 2 mmol/L of potassium, 0 g/L of glucose, different concentrations of sodium (mean 138 ± 0.9 mmol/L), ionized calcium (1.50 mmol/L), and dicarbonate (35.3 ± 2.4 mmol/L). Blood flow was set at 200–300 mL/min, ultrafiltration at 0–5 kg, and the duration of each dialysis at 4–5 hours. Diagnostic criteria for AVF dysfunction are as follows [12]: (i) disappearance of fistula murmur on clinical auscultation; (ii) weakening or disappearance of pulse at the fistula; (iii) diagnosis of fistula thrombosis by ultrasound; and (iv) blood flow <150 mL/min during dialysis.

Serum Magnesium Measurements

Blood samples for magnesium analysis were collected between 8:00 AM and 10:00 AM to minimize the effects of diurnal variation. Venous blood (5 mL) was drawn from each participant into trace element-free tubes containing ethylenediaminetetraacetic acid (EDTA) as an anticoagulant. Samples were immediately placed on ice and centrifuged at 3000 rpm for 10 minutes within one hour of collection to separate and obtain the plasma. Aliquots of the separated plasma were then packed into polypropylene tubes and stored at –80 °C for further analysis.

Serum magnesium levels were determined using an inductively coupled plasma mass spectrometry (ICP-MS) system, which is a highly sensitive and specific method of trace element analysis. The calibration method for this ICP-MS system involved the use of a multipoint calibration curve constructed daily from certified reference materials. This daily calibration ensures that the system remains accurate and reliable throughout the analysis process. The reliability of the calibration method was further validated by the consistent performance of the system, as evidenced by the low coefficients of variation observed in the quality control samples.

Quality control samples, including low- and high-level controls (both from the National Institute of Standards and Technology [NIST]), were analyzed with each batch of samples to ensure assay precision and accuracy. The coefficient of variation for quality control was kept within 5%. This strict quality control protocol ensures that the magnesium measurements are both precise and reliable.

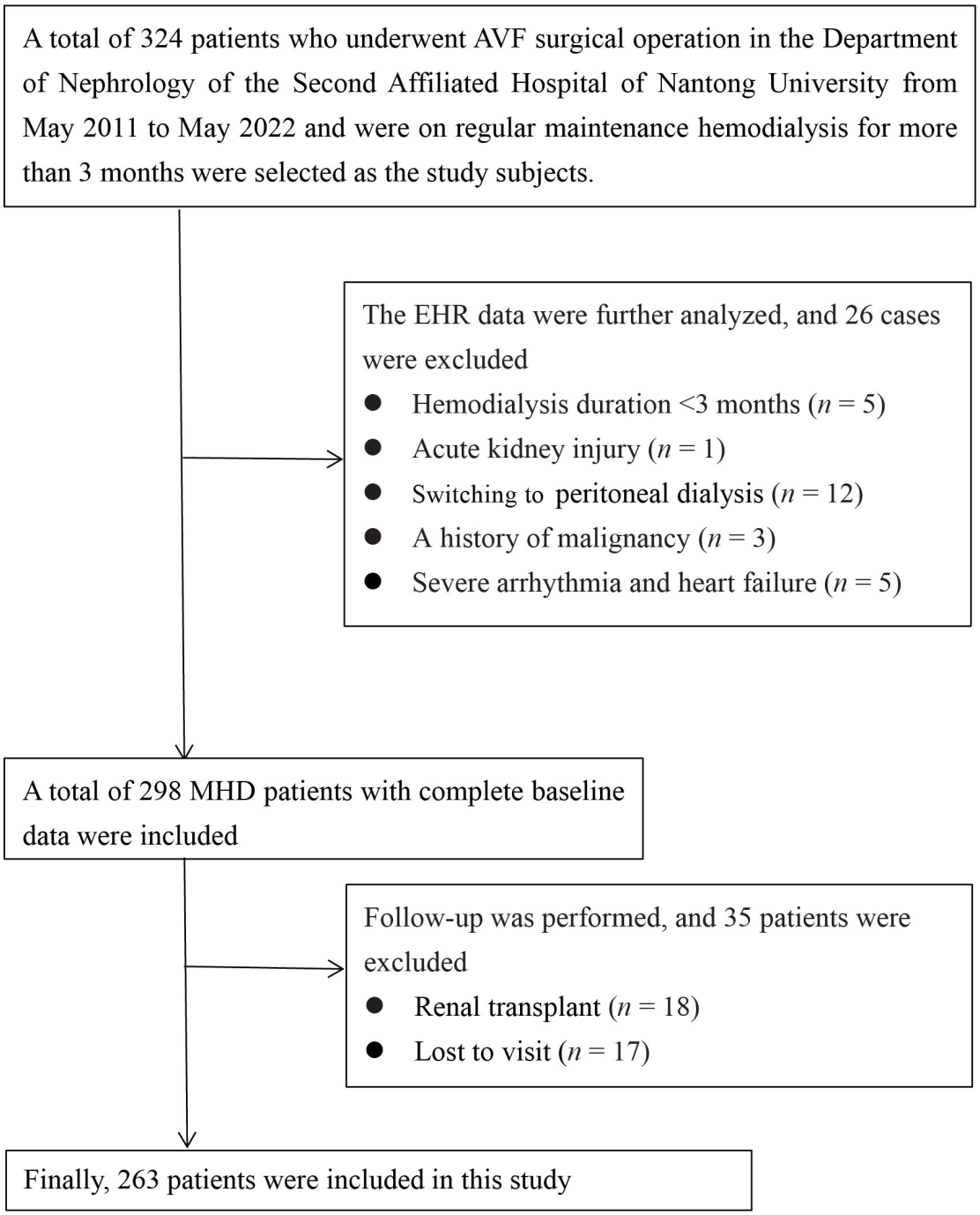

Fig. 1. Flowchart of study participant selection. Abbreviations: AVF, arteriovenous fistula; EHR, electronic health record; MHD, maintenance hemodialysis.

Study Endpoint

The current study analyzed the retrospective data collected from patients until 30 November 2022. The primary endpoint of interest was AVF dysfunction.

Statistical Analysis

The data were subjected to statistical analysis using the SPSS (version 25.0, IBM Corp., Armonk, NY, USA) and MedCalc (version 19.1, MedCalc Software, Ostend, Belgium) software packages. The sample size was estimated using the Statistical Analysis System (SAS, version 9.4, SAS Institute Inc., Cary, NC, USA), with an alpha level of 0.05 and a beta level of 0.1, a 20% shedding rate, and a minimum sample size of 98 cases. Data normality was determined using the D'Agostino & Pearson test. Normally distributed continuous variables are expressed as mean ± standard deviation (SD). For these variables, a two-sample *t*-test was used for between-group comparisons. Continuous variables with a non-normal distribution, as identified by the same test, are expressed as median (first quartile,

third quartile). For these variables, and a Mann–Whitney U test was used for between-group comparisons. Categorical variables are expressed as frequency and percentage, and between-group comparisons were performed using the chi-square test. In this study, we used the receiver operating characteristic (ROC) curve and Youden index to determine the optimal magnesium level cutoff for predicting AVF dysfunction in patients on MHD. The Youden index was calculated as the difference between the true positive rate (sensitivity) and the false positive rate (1-specificity) at each threshold. The optimal cutoff point was determined as the threshold that maximizes the Youden index, which is given by the formula: Youden index = Sensitivity + Specificity – 1. The patients were divided into two groups based on the serum magnesium cutoff value, designated as the high and low magnesium groups. The survival time in each group was estimated using Kaplan–Meier curves and a log-rank test was conducted for comparison between groups. The risk of AVF dysfunction was analyzed using logistic regression, and the results are expressed as odds ratio (OR) and 95% confidence interval (CI). The relationship between serum magnesium level and AVF dysfunction was analyzed using a Cox proportional hazard regression model, with the correlation with AVF dysfunction analyzed as a categorical variable. The results are expressed as a hazard ratio (HR) and a 95% CI. In this study, the significance level was set at $p < 0.05$, and a two-sided test was used for all statistical analyses.

Results

Baseline Information

A total of 263 patients, with a median age of 61 (48, 70) years, were included in the study. There were 164 male subjects (62.4%), and median follow-up duration was 32 (14, 51) months. The primary diseases included 98 cases (37.26%) of chronic glomerulonephritis, 78 cases (29.66%) of diabetic nephropathy, 36 cases (13.7%) of hypertensive nephropathy, 22 cases (8.4%) of polycystic kidney disease, and 29 other cases (11%, including gouty nephropathy, lupus nephritis and Antineutrophil Cytoplasmic Antibody (ANCA)-related renal impairment). The 263 MHD patients were divided into dysfunction group (n = 95, 36.12%) and non-dysfunction group (n = 168, 63.88%) based on their AVF function. The proportion of patients with chronic glomerulonephritis in the AVF dysfunction group was significantly lower than that in the non-dysfunction group. Additionally, the patients in the dysfunction group were significantly older than the patients in the non-dysfunction group ($p < 0.05$). No significant differences were observed in gender, BMI, smoking ratio, SBP and DBP between the two groups ($p > 0.05$) (Table 1).

The serum creatinine and magnesium levels in the dysfunction group were significantly lower than those in the non-dysfunction group, while the serum calcium and hemoglobin levels were significantly higher than those in the non-dysfunction group (all $p < 0.05$). Other laboratory parameters were not significant ($p > 0.05$) (Table 2).

Predictive Value of Magnesium for AVF Dysfunction

To investigate the predictive value of magnesium for AVF dysfunction in MHD patients, the cutoff value of magnesium was determined by means of an ROC curve. The optimal magnesium threshold for predicting AVF dysfunction in MHD was identified as 0.88 mmol/L, with an area under the curve (AUC) of 0.768, a p-value less than 0.001, a sensitivity of 68.42%, a specificity of 77.38%, and a Youden index of 0.458 (Fig. 2).

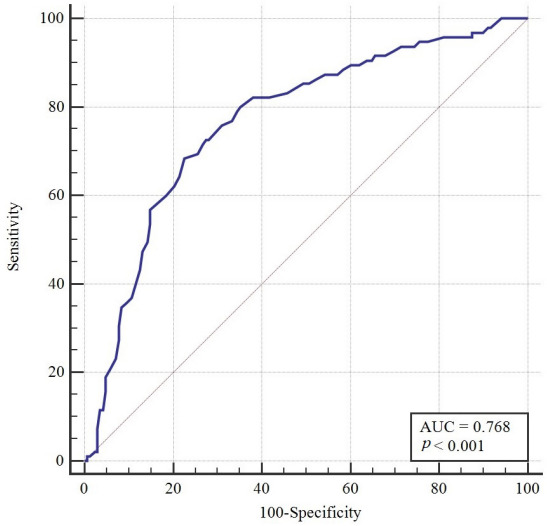

Fig. 2. ROC curve for serum magnesium in predicting AVF dysfunction in MHD patients. The ROC curve depicts the relationship between the true positive rate (TPR) and the false positive rate (FPR) at various threshold settings for predicting AVF dysfunction in MHD patients using serum magnesium levels. The AUC is a measure of the model's predictive accuracy, with values ranging from 0 (no discriminative power) to 1 (perfect prediction). An AUC of 0.768 indicates good discrimination, effectively distinguishing patients with AVF dysfunction from those without, and is close to the threshold of 0.8, which is associated with good diagnostic performance. Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic.

Patients were divided into two groups based on the cutoff value of magnesium: low magnesium (≤0.88 mmol/L) and high magnesium (>0.88 mmol/L). The AVF survival rate was compared between the two groups using the Kaplan–Meier method and the log-rank test. Censoring was managed by considering patients who did not experience AVF dysfunction or who were lost to follow-up as censored observations. The results of the Kaplan–Meier survival analysis indicated that the incidence of AVF dysfunction was significantly higher in the low magnesium group compared to the high magnesium group (log-rank $\chi^2 = 68.678$, $p < 0.001$) (Fig. 3).

Table 1. Comparison of baseline information between dysfunction group and non-dysfunction group.

Characteristics	Dysfunction group (n = 95)	Non-dysfunction group (n = 168)	$t/\chi^2/z$	p
Gender, n (%)				
Male	54 (32.93%)	110 (67.07%)	1.927	0.165
Female	41 (41.41%)	58 (58.59%)		
Age (years)	65.00 (56.00, 72.00)	56.00 (45.00, 68.00)	–12.180	<0.001
Primary disease				
Chronic glomerulonephritis	26 (27.37%)	72 (42.86%)	6.227	0.013
Diabetic nephropathy	34 (35.79%)	44 (26.19%)	2.680	0.102
Hypertensive nephropathy	10 (10.53%)	26 (15.48%)	1.258	0.262
Polycystic kidney disease	8 (8.42%)	14 (8.33%)	0.001	0.980
Others	17 (17.89%)	12 (7.14%)	7.151	0.008
BMI (kg/m^2)	23.88 (21.91–26.72)	23.60 (21.65–26.11)	–2.230	0.552
SBP (mmHg)	155.85 ± 18.17	158.42 ± 17.85	1.109	0.269
DBP (mmHg)	94.00 (81.00–101.00)	82.00 (71.00–94.75)	–3.920	0.261
Smoking ratio	13 (30.23%)	30 (69.77%)	0.773	0.379

Data are presented as n (%), mean ± standard deviation (SD), or median (first quartile, third quartile).

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

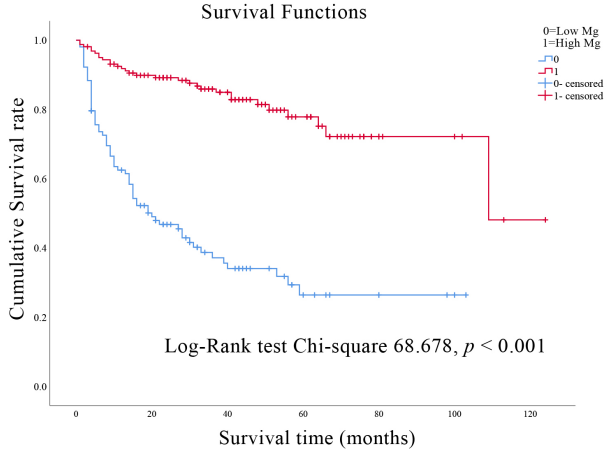

Fig. 3. Comparison of AVF survival rate in MHD patients between the high and low magnesium groups.

The logistic regression analysis demonstrated that the low magnesium group exhibited a 7.412-fold increased likelihood of developing AVF dysfunction in comparison to the high magnesium group (OR = 7.412, 95% CI, 4.218–13.025, $p < 0.001$). The adjusted model revealed that the risk of AVF dysfunction was 9.223 times higher in the low magnesium group than in the high magnesium group (Table 3).

The AVF Dysfunction Risk Model Assessment

The objective of this study is to examine the potential association between serum magnesium levels and AVF dysfunction. The follow-up period of this study was 32 months, with a range of 14 to 51 months. Univariate Cox regression analysis of potential predictors of AVF dysfunction in MHD patients revealed that age, chronic glomerulonephritis, serum creatinine, hemoglobin, calcium, and magnesium were associated with AVF dysfunction in patients ($p < 0.05$; Table 4). Multivariate Cox regression analysis demonstrated that age, calcium, hemoglobin and magnesium were independent risk factors for AVF dysfunction ($p < 0.01$; Fig. 4).

Magnesium was included in the Cox regression model as a categorical variables, with the high serum magnesium group (serum Mg ≥0.88 mmol/L) serving as the reference category. Four models were constructed using multiple Cox regression analysis. The results showed that the risk for AVF dysfunction in the low magnesium group was higher than that of the high magnesium group ($p < 0.001$), with the patients in the low magnesium group showing 4.534 times higher risk (HR = 4.534, 95% CI, 2.633–7.808; $p < 0.001$; Table 5).

Discussion

While human lifestyle is facing inevitable transformation, the aging of the population is getting more serious, and the incidence of CKD is increasing year by year, which seriously endangers health of the affected individuals. There are more than 1.5 million patients with ESRD worldwide, and the population is projected to grow further. Patients with ESRD retain a copious amount of toxic metabolites, which underlie the poisoning symptoms in digestive tract, blood, heart and other systemic structures. Currently, MHD is a primary renal replacement therapy for effectively removing toxins from the kidneys and prolonging patient survival [13]. AVF is the preferred vascular access for MHD patients, facilitating life maintenance and improving the quality and survival rate of life for these patients. However, reports indicate that the AVF patency rate is only 60% [14].

In this study, of 263 patients, the highest proportion of patients with chronic glomerulonephritis was 98 (37.26%)

Table 2. Comparison of laboratory results between dysfunction group and non-dysfunction group.

Characteristics	Dysfunction group	Non-dysfunction group	*t*/z	*p*
WBC ($\times 10^9$/L)	6.75 ± 2.45	6.83 ± 2.84	–0.246	0.806
Hb (g/L)	83.50 ± 20.03	77.0 ± 17.35	2.590	0.010
PLT ($\times 10^9$/L)	166.14 ± 47.21	156.05 ± 55.85	1.486	0.139
ALT (U/L)	15.06 ± 3.63	14.76 ± 4.22	0.596	0.552
AST (U/L)	16.55 ± 7.70	15.40 ± 7.28	1.200	0.231
AKP (U/L)	62.69 ± 20.03	63.28 ± 21.16	–0.223	0.824
Alb (g/L)	33.05 ± 5.18	33.17 ± 5.40	–0.175	0.861
TB (umol/L)	5.35 ± 1.81	5.17 ± 1.63	0.821	0.413
UA (umol/L)	508.02 ± 146.61	492.79 ± 133.61	0.857	0.392
β2-MG (mg/L)	14.25 (10.92, 21.18)	16.8 (12.00, 22.50)	–1.714	0.087
Scr (umol/L)	739.00 (633.00, 871.00)	806 (654.00, 1020.50)	–2.329	0.020
Cys-C (mg/L)	5.17 (4.40, 5.90)	5.20 (4.50, 6.08)	–0.842	0.400
TC (mmol/L)	4.15 ± 1.35	4.05 ± 1.29	0.567	0.571
TG (mmol/L)	1.42 ± 0.63	1.35 ± 0.56	0.927	0.355
HDL (mmol/L)	1.06 ± 0.27	1.02 ± 0.29	1.060	0.289
LDL (mmol/L)	2.27 (1.65–3.03)	2.28 (1.70–2.92)	–0.302	0.893
ApoA1 (g/L)	0.99 ± 0.24	0.98 ± 0.24	0.181	0.856
ApoB (g/L)	0.85 ± 0.30	0.85 ± 0.30	–0.100	0.919
hsCRP (mg/L)	6.88 (1.41, 16.24)	5.90 (0.88, 17.9)	–0.307	0.759
TSH (uIU/mL)	2.02 (0.94, 3.93)	2.11 (1.34, 3.66)	–0.430	0.667
Glu (mmol/L)	5.79 ± 1.97	5.44 ± 1.70	1.530	0.127
LDH (U/L)	258.62 ± 96.31	273.48 ± 98.84	–1.180	0.240
HBDH (U/L)	201.69 ± 73.31	211.89 ± 78.04	–1.030	0.303
K (mmol/L)	4.56 (4.00–5.25)	4.60 (4.08–5.06)	–0.113	0.992
P (mmol/L)	1.81 ± 0.46	1.88 ± 0.44	–1.298	0.196
Ca (mmol/L)	2.02 ± 0.23	1.94 ± 0.25	2.700	0.007
Mg (mmol/L)	0.85 ± 0.16	1.02 ± 0.19	–7.420	<0.001

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AKP, alkaline phosphatase; Alb, albumin; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; β2-MG, β2 microglobulin; TB, total bilirubin; Ca, serum calcium; Cys-C, cystatin C; Glu, blood glucose; Hb, hemoglobin; HBDH, alpha-hydroxybutyrate dehydrogenase; HDL, high-density lipoprotein cholesterol; hsCRP, hypersensitive C-reactive protein; K, serum potassium; LDH, lactate dehydrogenase; LDL, low density lipoprotein cholesterol; Mg, serum magnesium; P, serum phosphorus; PLT, platelets; Scr, serum creatinine; TC, total cholesterol; TG, triglyceride; TSH, thyroid stimulating hormone; UA, uric acid; WBC, white blood cell.

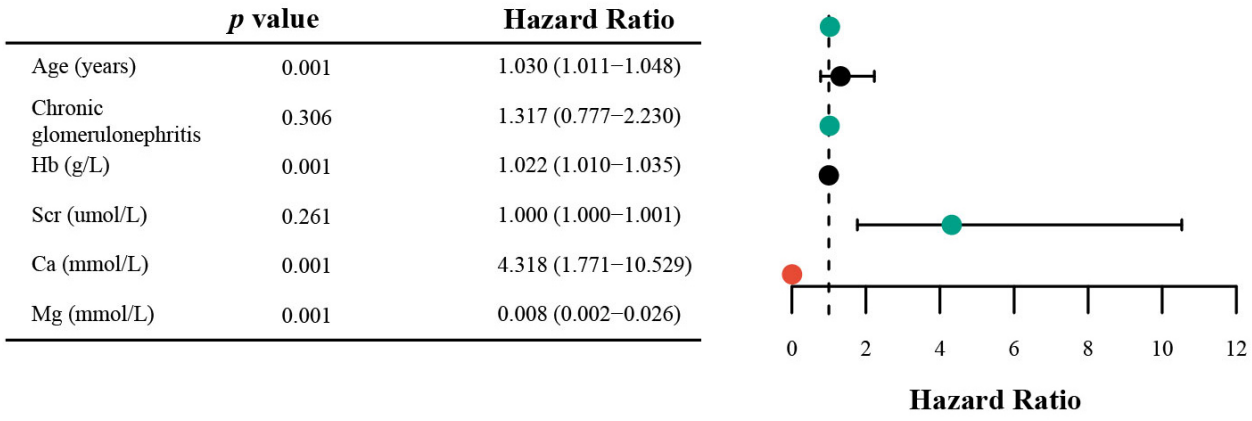

Fig. 4. Results of multivariate Cox regression analysis of AVF dysfunction.

Table 3. Unadjusted and multivariate-adjusted odds ratios for patients with AVF dysfunction and serum Mg ≤0.88 mmol/L.

Characteristics	Mg level		*p*
	Mg ≤0.88 mmol/L (n = 103)	Mg >0.88 mmol/L (n = 160)	
AVF dysfunction cases	65 (63.11%)	30 (18.75%)	
Unadjusted ORs (95% CI)	7.412 (4.218–13.025)	Reference	<0.001
Multivariate-adjusted ORs (95% CI)	9.223 (4.876–17.445)	Reference	<0.001

Note: Multivariate-adjusted ORs are yielded following the adjustments for age, hemoglobin, serum calcium, serum creatinine, and chronic glomerulonephritis.

Abbreviations: OR, odds ratio; CI, confidence interval.

Table 4. Results of univariate Cox regression analysis of influencing factors of AVF dysfunction in MHD patients.

Variables	β values	Standard error	Wald values	HR (95% CI)	*p*
Age (years)	0.029	0.009	10.27	1.032 (1.016–1.048)	<0.001
Gender, n (%)	–0.500	0.502	0.994	0.606 (0.227–1.621)	0.319
Primary disease					
Chronic glomerulonephritis	0.696	0.235	8.812	2.007 (1.267–3.178)	0.003
Diabetic nephropathy	0.588	0.443	1.760	1.800 (0.755–4.288)	0.185
Hypertensive nephropathy	–0.358	0.335	1.147	0.700 (0.362–1.348)	0.284
Polycystic kidney disease	0.892	0.534	2.760	2.44 (0.857–6.954)	0.126
BMI (kg/m^2)	0.015	0.28	0.027	1.015 (0.577–1.713)	0.869
SBP (mmHg)	–0.006	0.006	1.035	0.994 (0.983–1.005)	0.309
DBP (mmHg)	–0.007	0.007	1.00	0.993 (0.980–1.007)	0.317
Smoking ratio	–0.272	0.584	0.217	0.762 (0.243–2.393)	0.641
WBC ($\times 10^9$/L)	–0.009	0.039	0.048	0.992 (0.919–1.070)	0.827
Hb (g/L)	0.013	0.005	5.637	1.013 (1.002–1.024)	0.018
PLT ($\times 10^9$/L)	0.002	0.001	4.000	1.002 (0.999–1.004)	0.133
ALT (U/L)	0.012	0.026	0.203	1.012 (0.962–1.064)	0.652
AST (U/L)	0.013	0.012	1.165	1.013 (0.990–1.036)	0.28
AKP (U/L)	0.001	0.005	0.028	1.001 (0.991–1.011)	0.867
Alb (g/L)	–0.011	0.019	0.309	0.989 (0.952–1.028)	0.579
TB (μmol/L)	0.044	0.062	0.49	1.045 (0.924–1.181)	0.484
UA (μmol/L)	0.001	0.001	0.74	1.001 (0.999–1.002)	0.390
β2-MG (mg/L)	–0.012	0.013	0.851	0.988 (0.964–1.013)	0.356
Scr (μmol/L)	–0.001	0.000	5.904	0.999 (0.998–1.000)	0.015
Cys-C (mg/L)	–0.099	0.072	1.894	0.905 (0.786–1.043)	0.169
TC (mmol/L)	0.027	0.079	0.121	1.028 (0.881–1.199)	0.728
TG (mmol/L)	0.136	0.183	0.548	1.145 (0.800–1.640)	0.459
HDL (mmol/L)	0.299	0.334	0.801	1.348 (0.701–2.594)	0.371
LDL (mmol/L)	–0.027	0.104	0.069	0.973 (0.793–1.194)	0.793
ApoA1 (g/L)	–0.033	0.425	0.006	0.967 (0.420–2.226)	0.938
ApoB (g/L)	–0.145	0.35	0.173	0.865 (0.436–1.716)	0.678
hsCRP (mg/L)	–0.002	0.004	0.385	0.998 (0.990–1.005)	0.535
TSH (μIU/mL)	0.041	0.051	0.635	1.042 (0.942–1.152)	0.425
Glu (mmol/L)	0.076	0.049	2.435	1.079 (0.981–1.188)	0.119
LDH (U/L)	–0.002	0.001	4.000	0.998 (0.996–1.001)	0.169
HBDH (U/L)	–0.002	0.002	1.480	0.998 (0.995–1.001)	0.224
K (mmol/L)	0.053	0.124	0.186	1.055 (0.827–1.345)	0.666
P (mmol/L)	–0.461	0.218	4.483	0.670 (0.418–1.074)	0.096
Ca (mmol/L)	0.992	0.417	5.645	2.696 (1.190–6.108)	0.018
Mg (mmol/L)	–3.903	0.537	52.799	0.020 (0.007–0.058)	<0.001

Abbreviation: HR, hazard ratio.

Table 5. Relationship between serum magnesium and the risk of AVF dysfunction in MHD patients (multiple Cox regression equation).

Model	Low magnesium group (Mg ≤0.88 mmol/L)		High magnesium group (Mg >0.88 mmol/L)
	HR (95% CI)	*p*	
Model 1	5.291 (3.402–8.229)	<0.001	Reference
Model 2	5.178 (3.289–8.181)	<0.001	Reference
Model 3	5.063 (3.203–8.004)	<0.001	Reference
Model 4	4.534 (2.633–7.808)	<0.001	Reference

Notes: Model 1: Unadjusted; Model 2: Adjusted for age, sex, and primary disease; Model 3: Model 2 + Adjusted for smoking, BMI, and diabetes; Model 4: Model 3 + Adjusted for hemoglobin, calcium, creatinine, and dialysis age.

and diabetic nephropathy was 78 (29.66%). The proportion of patients with chronic glomerulonephritis in the AVF dysfunction group was significantly lower than in the non-dysfunction group ($p < 0.05$), while the incidence of diabetic nephropathy was not significantly different ($p > 0.05$). However, the multivariate Cox analysis revealed that chronic glomerulonephritis was not independently associated with AVF dysfunction ($p > 0.05$). Diabetic nitric oxide (NO) bioavailability abnormalities affect the maturation of AVF in most diabetic patients. In most cases, metabolic abnormalities may destroy the balance between the production of NO and its degradation. This can damage vascular endothelial cells, leading to lumen stenosis and thrombosis. Additionally, diabetes is a known independent risk factor for atherosclerosis, which can also affect the AVF blood flow [15,16]. However, previous studies reported that diabetes is not an independent risk factor for AVF immaturity and that diabetes does not influence AVF dysfunction and is not associated with early AVF thrombosis [17–19]. Therefore, it remains controversial as to whether diabetes can predict AVF loss because according to literature, AVF survival in diabetic patients is similar to that in non-diabetic patients, which is consistent with the results of this study [16]. In this study, age was an independent risk factor for AVF dysfunction ($p < 0.01$). It has been reported that elderly patients over 65 years had higher AVF dysfunction, because the elderly are more likely to experience vascular calcification and suffer many underlying diseases, thus requiring more intervention to maintain AVF patency [20,21].

In Cox analysis, elevated hemoglobin ($p < 0.001$)—which is consistent with some literature, indicating that the increase in hemoglobin concentration can mediate the increase of plasma viscosity—promotes thrombosis, and the increase of red cell aggregation can reduce microcirculation blood flow [22,23]. Moreover, the increase of hemoglobin concentration can increase the risk of cardiovascular events through hemodynamic or rheological mechanisms. Bashar *et al.* [24] found that lower hemoglobin promoted AVF maturation, which may be related to the ischemic hypoxia state, leading to increased synthesis of nitric oxide, and thus vasodilation. However, there are also many documents that elevated hemoglobin is not related to AVF dysfunction, or is even a protective factor [25,26]. Because the mortality rate of patients with lower hemoglobin is significantly increased, the correction of anemia may not improve the AVF dysfunction in patients.

In this study, serum calcium was significantly higher in AVF dysfunction group than in non-dysfunction group ($p < 0.01$), and serum calcium increase was an independent risk factor, according to the univariate Cox analysis ($p < 0.01$). However, in this study, phosphorus was not significantly associated with AVF dysfunction, which may be due to the insufficient sample size in this study. It is known that high calcium triggers more extensive deposition of calcium salt in the vascular wall, causing vascular wall calcification, intimal hyperplasia and abnormal intimal remodeling, and significantly increase the risk of death in patients with cardiovascular disease; separately, hyperphosphosphatemia not only causes vascular calcification, but also precipitates damage to endothelial cells, causing vascular stenosis [23]. High calcium and high phosphorus can cause cell matrix mineralization, which can lead to cell apoptosis, thereby promoting the development of vascular calcification [27–29]. Jankovic *et al.* [30] found that the annual patency rates of calcified AVF were significantly lower than those of non-calcified AVF. Allon *et al.* [31] believed that AVF vascular calcification was the prime reason affecting the maturation and use of AVF, which is consistent with this study.

In this study, AVF dysfunction rate was significantly higher in the low magnesium group than that in the high magnesium group (log-rank $\chi^2 = 68.678$, $p < 0.001$). Logistic regression analysis showed that the possibility of AVF dysfunction in the low magnesium group was 7.412 times that in the high magnesium group. Low magnesium was an independent risk factor for AVF dysfunction in both the uni- and multi-variate Cox analyses ($p < 0.001$). The risk of AVF dysfunction was 4.534 times higher in the low magnesium group than in the high magnesium group. It has been shown that MHD patients with low magnesium are prone to vascular calcification, and magnesium levels were lower in the vascular calcification group than in the avascular calcification group [32]. The reason may be that magnesium is calcium channel blocker that plays an important role in cardiovascular, neurological and metabolic functions, and magnesium deficiency leads to vascular stenosis, inflammatory response, oxidative stress, and vascular endothelial function impairment, which causes vascular calcification. In addition, low magnesium is associated with atherosclerosis, and some studies showed that magnesium level is negatively correlated with carotid intima-media thickness, which is an early and reliable marker of atherosclerosis [11,33–35]. In this study, we identified that a magnesium level of 0.88 mmol/L serves as the optimal threshold for

predicting AVF dysfunction in MHD patients, with an AUC of 0.768 and a *p*-value of less than 0.001. This suggests that low magnesium may act as a predictor of AVF dysfunction. Our findings indicate a potential role that magnesium plays in the development of vascular calcification and atherosclerosis in MHD patients, ultimately contributing to AVF dysfunction.

Although our study provides insights into the potential of serum magnesium in predicting AVF dysfunction, the retrospective nature of the study and the relatively small sample size may limit the generalizability of our findings. The lack of randomization and potential selection bias could introduce confounding variables that were not accounted for in our analysis. Future prospective, multicenter studies with larger sample sizes are needed to validate these results and to further explore the mechanisms underlying the observed associations.

Conclusions

In conclusion, our study confirms that low serum magnesium is a significant independent risk factor for AVF dysfunction in MHD patients, aligning with our primary objective of investigating the role of magnesium in AVF patency. This finding underscores the importance of monitoring and managing magnesium levels to improve AVF outcomes.

Availability of Data and Materials

The data analyzed are available from the corresponding author upon reasonable request.

Author Contributions

WBY, YS, LLS, XHW, HLY, JJC, LLM and HXH designed the research study; WBY, YS, LLS, XHW, HLY, JJC, LLM and HXH performed the research; WBY, YS, LLS, XHW, HLY, JJC, LLM and HXH collected and analyzed the data. WBY and YS have been involved in drafting the manuscript and all authors have been involved in revising it critically for important intellectual content. All authors give final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Board of The Second Affiliated Hospital of Nantong University with number 2022KT109 and conducted in accordance with the Declaration of Helsinki and China's regulations on clinical research. All study subjects voluntarily participated and provided written informed consent.

Acknowledgment

Not applicable.

Funding

This study is supported by Nantong Municipal Science and Technology Bureau (MSZ2022011), Basic Research Projects of Nantong (JC22022008), Medical Research Project of Nantong Health Commission (MS2022026), Medical Research Project of Nantong Health Commission (MS2023034).

Conflict of Interest

The authors declare no conflict of interest.

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