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Original Article

Prognostic significance of the hs-CRP/Alb ratio for cardiovascular events in patients with end-stage renal disease undergoing maintenance hemodialysis

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Abstract: Objective: To evaluate the predictive power of the high-sensitivity C-reactive protein (hs-CRP) to albumin (Alb) ratio for cardiovascular events in patients receiving maintenance hemodialysis (MHD) for end-stage renal disease (ESRD). Methods: This retrospective study enrolled 202 ESRD patients undergoing MHD at Bobai County People's Hospital from November 2020 to November 2022, with follow-up extending to November 2023. Patients were divided into two groups based on the occurrence of cardiovascular events during follow-up: the occurrence group (n = 92) and the non-occurrence group (n = 110). Clinical data were compared between these groups. Independent risk factors for cardiovascular events post-MHD were identified using a multivariate logistic regression model. The hs-CRP/Alb ratio's predictive utility was assessed through receiver operating characteristic (ROC) curve analysis, establishing an optimal cutoff value. A decision tree prediction model was developed to further delineate the probability of cardiovascular events. Results: The occurrence group was older and had a longer duration of dialysis compared to the non-occurrence group ($P < 0.05$). They also showed a higher prevalence of diabetic and hypertensive nephropathy and a higher proportion of smokers (all $P < 0.05$). Notably lower levels of hemoglobin (HGB), triglycerides, total cholesterol, low-density lipoprotein, albumin (Alb), and calcium were detected (all $P < 0.05$), whereas β2-microglobulin (β2-mg), hs-CRP, phosphorus, and the hs-CRP/Alb ratio were markedly increased (all $P < 0.05$). Multivariate analysis revealed diabetic nephropathy or hypertensive nephropathy, a high hs-CRP/Alb ratio, and elevated phosphorus levels as risk factors for cardiovascular events, while high hemoglobin levels were protective ($P < 0.05$). The ROC analysis indicated the hs-CRP/Alb ratio (AUC = 0.884) outperformed other predictors with an optimal cutoff at 0.111. Patients with a hs-CRP/Alb ratio ≥ 0.111 were found to have a 29-fold increased risk of cardiovascular events (95% CI: 11.304-74.842). Conclusion: The hs-CRP/Alb ratio is a significant predictive biomarker for cardiovascular events in ESRD patients undergoing MHD. An elevated hs-CRP/Alb ratio is associated with an increased risk of cardiovascular events, underscoring its utility in this patient population.

Keywords: High-sensitivity C-reactive protein/albumin ratio, maintenance hemodialysis, cardiovascular events, predictive value

Introduction

Patients with chronic kidney disease (CKD) often require maintenance hemodialysis (MHD) when their condition progresses to end-stage renal disease (ESRD). MHD extends survival by filtering and purifying blood extracorporeally. However, long-term dialysis is associated with a higher incidence of cardiovascular events, such as angina pectoris, myocardial infarction, and sudden cardiac death, which are major causes of mortality in these patients [1]. Cardiovascular events are responsible for approximately 45% of all deaths among patients with ESRD [2, 3]. Therefore, early prediction of these events following MHD is crucial for improving outcomes and reducing mortality.

Inflammation links CKD to cardiovascular disease and mediates the development of cardiovascular complications in CKD patients [4]. High-sensitivity C-reactive protein (hs-CRP) and albumin (ALB), both synthesized in the liver, serve as markers of inflammation. Prior studies

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have established the importance of hs-CRP and ALB in the progression of inflammatory and infectious diseases [5, 6]. The hs-CRP/ALB ratio, a novel inflammatory marker studied in recent years, has demonstrated predictive value for the acute exacerbation of chronic diseases and various inflammation-related conditions [7, 8]. However, few studies have explored its effectiveness in predicting cardiovascular events in patients with ESRD undergoing MHD. Thus, this study aims to investigate the predictive utility of the hs-CRP/ALB ratio for cardiovascular events in these patients, providing a reference for early symptomatic treatment.

Materials and methods

General information

This retrospective study was conducted at Bobai County People's Hospital from November 2020 to November 2022. A total of 202 patients with ESRD who initiated MHD for the first time were enrolled and followed until November 2023. Inclusion Criteria: (1) Patients diagnosed with ESRD according to established criteria [9]. (2) Age ≥ 18 years old. (3) Availability of complete clinical data, including follow-up records, laboratory results, and data related to diagnosis and treatment.

Exclusion criteria: (1) Patients with a previous history of renal transplantation or peritoneal dialysis. (2) Presence of active inflammation, recent trauma, surgery, or severe liver dysfunction. (3) Concurrent hematologic diseases, such as aplastic anemia. (4) Presence of malignant tumors. (5) Acute and chronic severe infections. (6) Active autoimmune diseases or use of hormones and immunosuppressants.

All patients underwent hemodialysis using bicarbonate dialysate and a disposable polysulfone membrane dialyzer with a membrane area of 1.5 m^2. Blood flow rates were maintained between 180 to 250 mL/min, and dialysate flow was set at 500 mL/min, with weekly dialysis sessions lasting between 10 to 12 hours. The anticoagulants used were either heparin sodium injection or low molecular weight heparin, tailored by healthcare professionals according to individual patient needs and in accordance with clinical guidelines. The study received approval from the Medical Ethics Committee of Bobai County People's Hospital.

Data collection

General data: Demographic and baseline data were collected for all enrolled patients at the initiation of dialysis. This included gender, age, smoking history, primary etiology of renal disease (chronic nephritis, diabetic nephropathy, hypertensive nephropathy, obstructive nephropathy, other), and specific cardiovascular events occurring during the follow-up period.

Laboratory indicators: Upon admission, a routine blood examination was conducted using a blood cell analyzer (XN9000, Sysmex, Japan) to measure hemoglobin (HGB, g/L). Additionally, 8 ml of fasting peripheral venous blood was drawn before the first dialysis session and centrifuged to separate the serum. The levels of blood urea nitrogen (BUN, mg/dl), serum creatinine (Scr, umol/L), β2-microglobulin (β2-MG, mg/L), albumin (Alb, g/L), potassium, calcium, phosphorus (mmol/L), triglycerides (TG, mmol/L), total cholesterol (TC, mmol/L), high-density lipoprotein (HDL, mmol/L), and low-density lipoprotein (LDL, mmol/L) were determined using an automatic biochemistry analyzer (AU5800, Beckman, USA). Serum levels of parathyroid hormone (PTH, pg/mL) were measured using a parathyroid hormone assay kit (Roche, Germany, Lot number: (10)70635603). Concentrations of serum hs-CRP (mg/L) were measured using a hs-CRP assay kit (*MeiKangShengWu, China,* Lot number: 231211101). The hs-CRP/Alb ratio and the calcium-phosphorus product were calculated thereafter. All clinical data were sourced from the clinical case and examination systems of Bobai County People's Hospital.

Follow-up visit

Patients were monitored every two months via outpatient reviews or telephone calls until November 2023, with cardiovascular events serving as the primary endpoint. Cardiovascular events were defined as hospitalization due to acute myocardial infarction, unstable angina, congestive heart failure, transient ischemic attack, stroke, percutaneous coronary intervention, peripheral atherosclerosis, or cardiovascular death, as recorded in clinical records [10]. Patients were categorized into groups based on the occurrence or absence of cardiovascular events during the follow-up period.

Table 1. Comparison of the general information [$\bar{x}$±sd, M(P25, P75), n (%)]

Basic data	Non-occurrence group (n = 110)	Occurrence group (n = 92)	x^2/t/z value	*P* value
Gender (Male/female)	66 (60.00)/44 (40.00)	60 (65.22)/32 (34.78)	0.581	0.446
Age (years)	52.76±14.07	60.82±13.28	4.156	< 0.001
Dialysis age (months)	11.00 (5.00, 21.50)	17.50 (9.25, 33.00)	-3.215	0.001
Type of PRIMARY disease			19.693	0.001
Chronic nephritis	62 (56.36)	28 (30.43)		
Diabetic nephropathy	20 (18.18)	31 (33.70)		
Hypertensive nephropathy	7 (6.37)	18 (19.57)		
Obstructive nephropathy	13 (11.82)	10 (10.87)		
Other Types	8 (7.27)	5 (5.43)		
Smoking (no/yes)	87 (79.09)/23 (20.91)	50 (54.35)/42 (45.65)	14.054	< 0.001

Statistical analysis

Statistical analyses were conducted using SPSS version 23.0. Measurement data following a normal distribution were described as mean ± standard deviation ($\bar{x}$±sd) while data not following a normal distribution were expressed as the median and interquartile range (M(P25, P75)). Inter-group comparisons were performed using the t-test and the Mann-Whitney U Test for normally and non-normally distributed data, respectively. Categorical data were presented as n (%) and analyzed using the chi-square test. Multivariate logistic regression was employed to examine factors influencing cardiovascular events following MHD treatment in patients with ESRD. The predictive value of serum hs-CRP, Alb, the hs-CRP/Alb ratio, and other factors for cardiovascular events was assessed using the receiver operating characteristic (ROC) curve; this included calculating the area under the curve (AUC) and determining cutoff values. Decision tree analysis was conducted using the "rpart" package in R software version 4.2.3 to identify key predictors of cardiovascular events in these patients. A *p*-value < 0.05 was considered statistically significant.

Result

Incidence of cardiovascular events

Among the 202 enrolled ESRD patients receiving MHD, 92 experienced cardiovascular events such as chronic cardiac insufficiency and coronary heart disease during the follow-up period, corresponding to an event rate of 45.54% (92/202). These patients were categorized into the occurrence group, while the 110 patients who did not experience cardiovascular events were categorized into the non-occurrence group.

Comparison of basic information

Basic demographic and clinical data comparisons revealed that the occurrence group was older and had a longer duration of dialysis compared to the non-occurrence group (P < 0.05). The prevalence of diabetic nephropathy, hypertensive nephropathy, and smoking was significantly higher in the occurrence group, while the incidence of chronic nephritis was lower compared to the non-occurrence group (P < 0.05), as shown in **Table 1**.

Comparison of the laboratory test results

The comparative analysis of laboratory results revealed that the occurrence group exhibited lower levels of HGB, TG, TC, LDL, Alb and calcium compared to the non-occurrence group. Conversely, levels ofβ2-MG, hs-CRP, the hs-CRP/Alb ratio, and phosphorus were higher in the occurrence group (all P < 0.05), as detailed in **Table 2**.

Multivariate logistic regression analysis

The multivariate logistic regression analysis was performed to identify factors influencing the occurrence of cardiovascular events. The dependent variable was the presence of cardiovascular events (non-occurrence = 0, occurrence = 1). Independent variables included in the model were types of primary disease (0 = chronic nephritis, 1 = diabetic nephropathy, 2 = hypertensive nephropathy, 3 = obstructive nephropathy, 4 = others), smoking status (0 = no, 1 = yes), age, duration of dialysis, levels of

Table 2. Comparison of the outcomes of laboratory tests [$\bar{x}$±sd, M(P25, P75), n (%)]

Laboratory test results	Non-occurrence group (n = 110)	Occurrence group (n = 92)	x^2/t/z value	*P* value
HGB (g/L)	113.75±19.08	94.65±19.63	-6.991	< 0.001
PTH (pg/mL)	190.45 (102.70, 328.43)	216.90 (112.50, 397.38)	-0.733	0.463
β2-MG (mg/L)	20.46 (15.37, 24.11)	23.20 (19.38, 30.42)	-3.508	< 0.001
BUN (mg/dl)	15.90 (12.10, 20.49)	16.95 (13.30, 21.88)	-1.374	0.169
Scr (umol/L)	644.20 (491.75, 828.25)	651.40 (508.33, 819.05)	-0.283	0.777
TG (mmol/L)	1.48 (0.98, 1.96)	1.09 (0.79, 1.78)	-2.826	0.005
TC (mmol/L)	4.22 (3.53, 5.03)	3.88 (3.11, 4.54)	-2.612	0.009
HDL (mmol/L)	1.14 (0.91, 1.44)	1.10 (0.81, 1.37)	-1.280	0.200
LDL (mmol/L)	2.39 (1.91, 3.05)	2.12 (1.66, 2.57)	-2.613	0.009
hs-CRP (mg/L)	1.82 (0.87, 3.53)	7.68 (4.74, 12.83)	-8.944	< 0.001
Alb (g/L)	42.66±3.80	36.06±4.82	-10.885	< 0.001
hs-CRP/Alb	0.04 (0.02, 0.08)	0.21 (0.12, 0.37)	-9.382	< 0.001
Potassium (mmol/L)	4.29±0.66	4.45±1.08	1.307	0.193
Calcium (mmol/L)	2.21±0.19	2.13±0.27	-2.184	0.030
P (mmol/L)	1.26 (1.03, 1.68)	1.46 (1.21, 1.98)	-2.766	0.006
Calcium and phosphorus product (mg/dl)	2.78 (2.27, 3.59)	3.08 (2.36, 3.87)	-1.842	0.066

Notes: HGB: Hemoglobin, PTH: Parathyroid hormone, BUN: Blood urea nitrogen, β2-MG: Beta 2 microglobulin, TG: Triglycerides, TC: Total cholesterol, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Scr: Serum creatinine, hs-CRP: High-sensitivity C-reactive protein, Alb: albumin, P: phosphorus.

Table 3. Multivariate logistic regression analysis

Variables of interest	B value	SE value	Wald value	*P* value	OR value (95% CI)
The primary disease was diabetic nephropathy	1.379	0.662	4.337	0.037	3.969 (1.085-14.528)
The primary disease was hypertensive nephropathy	1.605	0.808	3.950	0.047	4.980 (1.022-24.254)
HGB (g/L)	-0.046	0.016	8.155	0.004	0.955 (0.926-0.986)
hs-CRP/Alb	1.771	0.363	23.793	< 0.001	5.872 (2.883-11.958)
P (mmol/L)	2.097	0.617	11.545	0.001	8.142 (2.429-27.296)

Notes: HGB: Hemoglobin, hs-CRP: High-sensitivity C-reactive protein, Alb: albumin, P: phosphorus.

HGB, β2-MG, TG, TC, LDL-C, the hs-CRP/Alb ratio, calcium, and phosphorus. Given that the hs-CRP/Alb ratio is derived from Alb and hs-CRP, these individual components were excluded from the regression to avoid multicollinearity. The analysis revealed that diabetic nephropathy or hypertensive nephropathy, a high hs-CRP/Alb ratio, and elevated phosphorus levels were risk factors for cardiovascular events ($P < 0.05$), while a higher level of HGB served as a protective factor ($P < 0.05$). See **Table 3** for details.

ROC curve analysis of predictive value of hs-CRP/Alb ratio for cardiovascular events

To assess the predictive ability of hs-CRP, Alb, hs-CRP/Alb, HGB, phosphorus, and primary disease type for cardiovascular events in patients with ESRD undergoing MHD, ROC curve analysis was employed. The AUC demonstrated significant predictive efficacy for all tested parameters: hs-CRP achieved an AUC of 0.866 (95% CI: 0.813-0.918), Alb reached 0.860 (95% CI: 0.808-0.911), and the hs-CRP/Alb ratio was 0.884 (95% CI: 0.834-0.933). HGB, phosphorus, and primary disease type had AUCs of 0.760 (95% CI: 0.694-0.827), 0.613 (95% CI: 0.534-0.692), and 0.605 (95% CI: 0.527-0.684), respectively (all $P < 0.05$). The hs-CRP/Alb ratio exhibited the strongest predictive power with a critical cutoff value of 0.111. See **Table 4** and **Figure 1** for details.

Patients were divided into two groups based on the hs-CRP/Alb ratio: ≥ 0.111 and < 0.111.

Table 4. ROC curve analysis of influencing factors predicting cardiovascular events after MHD treatment in patients with ESRD

Factors	AUC	Sensitivity	Specificity	Critical value	95% CI	*P* value
hs-CRP	0.866	0.750	0.864	4.850 mg/L	0.813-0.918	< 0.001
Alb	0.860	0.818	0.793	39.850 g/L	0.808-0.911	< 0.001
hs-CRP/Alb	0.884	0.793	0.873	0.111	0.834-0.933	< 0.001
HGB	0.760	0.755	0.652	101.5 g/L	0.694-0.827	< 0.001
P	0.613	0.261	0.955	1.95 mmol/L	0.534-0.692	0.040
Type of PRIMARY disease	0.605	0.696	0.564	--	0.527-0.684	0.010

Notes: HGB: Hemoglobin, hs-CRP: High-sensitivity C-reactive protein, Alb: albumin, P: phosphorus, AUC: Area under the ROC curve, 95% CI: 95% confidence interval, ESRD: end-stage renal disease.

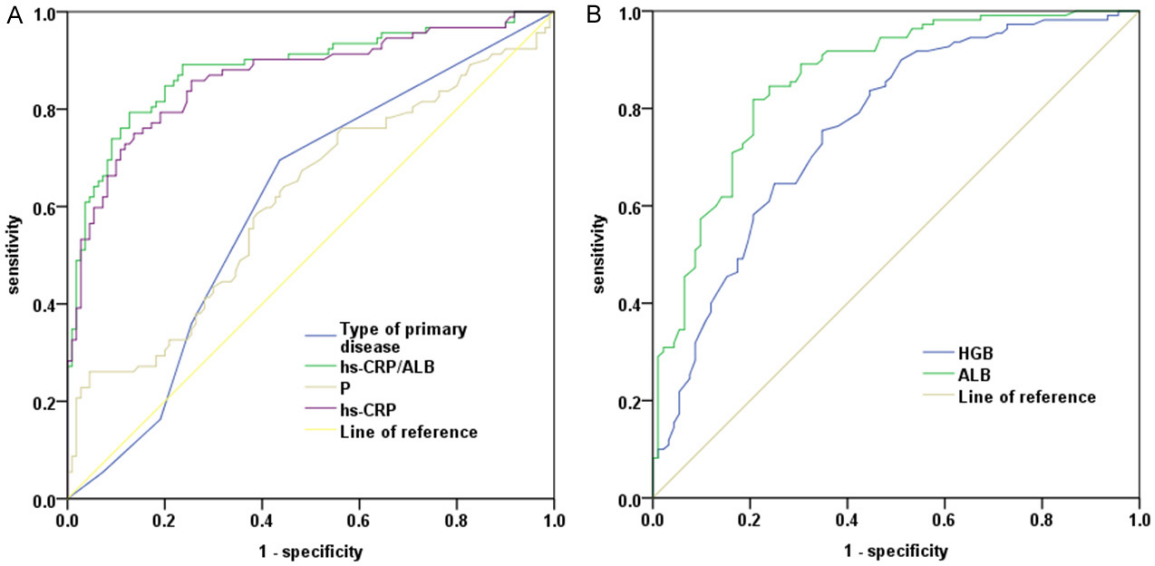

Figure 1. ROC curve analysis for predicting cardiovascular events in patients with ESRD receiving MHD therapy. A: ROC curves for primary disease type, hs-CRP/Alb ratio, P, and hs-CRP; B: ROC curves for HGB and ALB. Notes: HGB: Hemoglobin, hs-CRP: High-sensitivity C-reactive protein, Alb: albumin, P: phosphorus, ESRD: end-stage renal disease.

Binary logistic regression analysis was conducted using the incidence of cardiovascular events as the dependent variable. Before adjustment, the risk of cardiovascular events in the hs-CRP/Alb ratio ≥ 0.111 group was 26.346 times higher than in the hs-CRP/Alb ratio < 0.111 group (95% CI: 12.390-56.024). After adjusting for primary disease type, phosphorus, and HGB, the risk increased to 29.087 times (95% CI: 11.304-74.842), as indicated in **Table 5**.

Decision tree modeling to identify patients at high risk for cardiovascular events

A decision tree prediction model was developed incorporating primary disease type, phosphorus, HGB, and hs-CRP/Alb to predict the occurrence of cardiovascular events. The model identified three significant predictors: hs-CRP/Alb, HGB, and phosphorus. The hs-CRP/Alb ratio had the most substantial first-order influence on the risk of cardiovascular events, with an optimal cutoff point of 0.111 determined as the initial split variable, as detailed in **Figure 2**.

Discussion

CKD and cardiovascular disease frequently coexist, particularly in patients with ESRD undergoing MHD, where the incidence of cardiovascular disease is notably higher, and prognosis often poor [11]. Consequently, the identi-

Table 5. Unadjusted and multileveled-adjusted OR values for cardiovascular events in patients with ESRD with hs-CRP/Alb ratio ≥ 0.111 (95% CI)

Item	hs-CRP/Alb ratio		*P* value
	≥ 0.111 (n = 87)	< 0.111 (n = 115)	
Cardiovascular events (%)	73 (83.91)	19 (16.52)	< 0.001
Unadjusted OR (95% CI)	26.346 (12.390-56.024)	Reference value	< 0.001
Multilevel (primary disease type +P+HGB) adjusted OR (95% CI)	29.087 (11.304-74.842)	Reference value	< 0.001

Notes: HGB: Hemoglobin, hs-CRP: High-sensitivity C-reactive protein, Alb: albumin, P: phosphorus, OR: Odds Ratio, ESRD: end-stage renal disease.

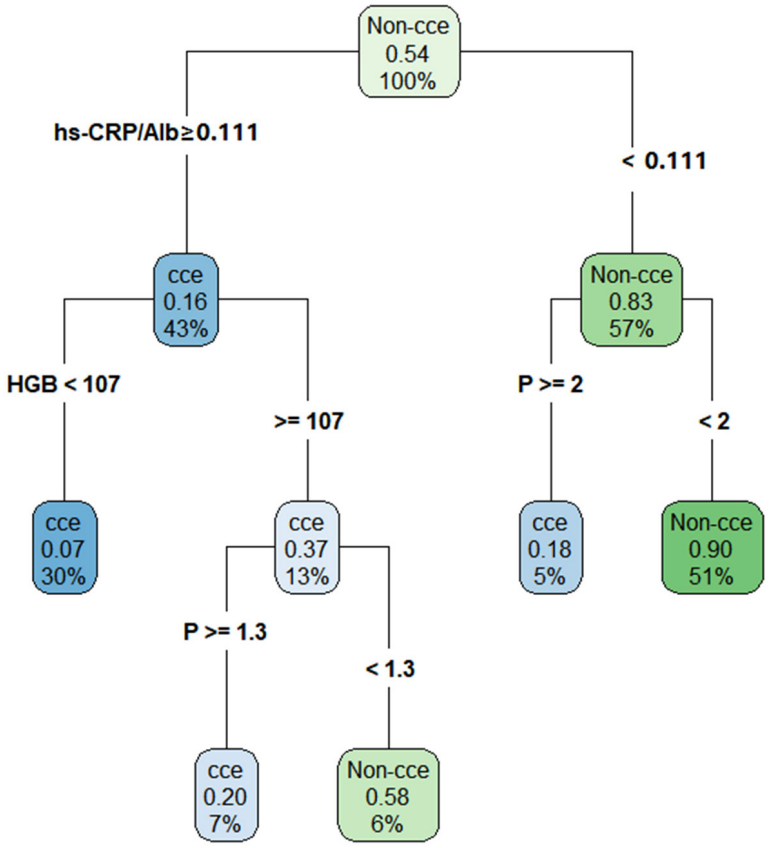

Figure 2. Decision tree model of cardiovascular events in patients with ESRD treated with MHD. Notes: HGB: Hemoglobin, hs-CRP: High-sensitivity C-reactive protein, P: phosphorus, cce: cardiovascular events.

fication of safe, simple, and validated methods to predict cardiovascular events post-MHD and to implement early interventions is crucial for improving outcomes in this population.

Traditional risk factors such as age, smoking, diabetes, and dyslipidemia are well-known, but non-traditional factors like oxidative stress, microinflammation, hypoproteinemia, malnutrition, anemia, and disorders of calcium and phosphorus metabolism, including elevated parathyroid hormone levels, also play significant roles in the pathogenesis of cardiovascular disease in patients treated with MHD [12-14]. Numerous studies have highlighted chronic inflammation as a critical factor in both the development and progression of cardiovascular events in dialysis patients, underscoring the importance of clinically available inflammatory markers for predicting prognosis [15, 16].

CRP is an acute-phase protein produced in response to inflammation, capable of mediating the effects of tumor necrosis factor and interleukin-6, and is often elevated in conditions involving tissue injury, local ischemia, inflammatory defense responses, and acute infections [17]. hs-CRP is a more specific and sensitive marker of inflammation, influencing immune system modulation and enhancing macrophage activity and mobility, thereby increasing their phagocytic action against various foreign substances. Alb, another acute-phase reactant, reflects the body's nutritional status; low levels indicate not only malnutrition but also a systemic inflammatory response [18]. The hs-CRP/Alb ratio, as an emerging inflammatory marker, has increasingly been used to predict the acute onset of chronic diseases, and is currently regarded as a prognostic indicator for conditions such as cerebral infarction and sepsis [19, 20].

Qin et al. [21] observed that patients with ESRD who developed cardiovascular events post-

MHD treatment exhibited higher levels of hs-CRP compared to those who did not develop such events. Consistently, our study found elevated hs-CRP levels, a higher hs-CRP/Alb ratio, and decreased Alb levels in ESRD patients who experienced cardiovascular events after MHD treatment. Moreover, an increased hs-CRP/Alb ratio was identified as a significant risk factor for the development of cardiovascular events in this patient cohort, underscoring that a higher ratio correlates with an elevated risk of these events. The potential mechanisms include vascular endothelial injury and enhanced permeability due to a heightened inflammatory state, which may exacerbate vascular complications [22].

Further supporting this, a study reported that a high hs-CRP/Alb ratio at the onset of hemodialysis significantly correlated with an increased risk of mortality within the first six months, primarily due to cardiovascular events [23]. This finding aligns with our study, reinforcing the hs-CRP/Alb ratio as a critical risk factor for cardiovascular events in patients undergoing MHD.

Additionally, Stenvinkel et al. [24] first proposed the concept of malnutrition, inflammation, and atherosclerosis syndrome in uremic patients in 1999, highlighting the interplay of these factors in chronic renal failure with inflammation as a central component. Contrarily, another study noted that hs-CRP levels in MHD patients decreased with increasing dialysis duration, correlating with improved nutritional status. It was found that hs-CRP was significantly negatively associated with Alb levels, indicating that a lower Alb level has a more detrimental impact on the prognosis of hemodialysis patients than a higher hs-CRP level. Such discrepancies may stem from the observational nature of these studies, where the lack of randomization and uneven distribution of confounding factors might introduce biases [25].

Further ROC curve analysis demonstrated that the hs-CRP/Alb ratio had the highest AUC of 0.884, with a sensitivity of 0.793 and specificity of 0.873, outperforming hs-CRP, Alb, HGB, phosphorus, and primary disease type in predicting cardiovascular events in patients with ESRD undergoing MHD. The decision tree model also identified the hs-CRP/Alb ratio as the primary determinant of cardiovascular events in this patient group. These findings highlight the efficacy of the hs-CRP/Alb ratio in predicting cardiovascular events following MHD therapy in patients with ESRD.

In a study involving 2,437 individuals experiencing their first episode of ST-segment elevation myocardial infarction who underwent primary percutaneous coronary intervention, the hs-CRP/Alb ratio was identified as an independent predictor of all-cause mortality, exhibiting superior predictive performance compared to hs-CRP and Alb alone [26]. This ratio has also been recognized as an independent predictor of severe peripheral artery disease [27]. These findings indirectly corroborate the utility of the hs-CRP/Alb ratio in forecasting cardiovascular events following MHD treatment.

The optimal threshold value of the hs-CRP/Alb ratio for predicting cardiovascular events in ESRD patients' post-MHD treatment was determined to be 0.111. When the pre-treatment hs-CRP/Alb ratio exceeds this value, the risk of cardiovascular events significantly increases, with a 29.087-fold higher risk (95% CI: 11.304-74.842). This significant impact underscores the importance of this ratio in the occurrence of cardiovascular events. Therefore, clinicians can use this threshold as a reference when assessing the risk of cardiovascular events among ESRD patients undergoing MHD, to determine the need for further testing or intervention.

This study has several limitations. Firstly, it is a retrospective analysis conducted at a single center with a relatively small sample size, and the follow-up period is limited. To validate our findings, it is necessary to include cases from multiple hemodialysis centers, increase the sample size, and extend the duration of follow-up observations. Secondly, while we excluded cases with diseases that directly influence hs-CRP and Alb levels, there are numerous factors affecting these biomarkers, making it challenging to completely eliminate the impact of confounding variables.

In summary, the hs-CRP/Alb ratio in patients with ESRD undergoing MHD emerges as a significant risk factor for cardiovascular events. It demonstrates substantial predictive value for such events post-MHD. A high hs-CRP/Alb ratio indicates an increased risk of cardiovascular events, suggesting its potential utility in

clinical risk assessment and management strategies.

Disclosure of conflict of interest

None.

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