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ORIGINAL RESEARCH

Clinical Characteristics and Risk Factors for Major Adverse Cardiovascular Events in Patients on Maintenance Hemodialysis: A Retrospective Study

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Objective: Patients on maintenance hemodialysis face a disproportionately high burden of cardiovascular disease, with major adverse cardiovascular events being the leading cause of death. However, the relative importance and specific roles of traditional versus non-traditional risk factors in this unique population require further elucidation in clinical practice. This study aimed to investigate the risk factors for major adverse cardiovascular events in patients undergoing maintenance hemodialysis, thereby providing evidence for clinical risk stratification and early intervention.

Methods: A single-center retrospective study was carried out, enrolling 196 patients with end-stage renal disease who received regular MHD (duration ≥ 6 months) between January 2021 and August 2022. According to MACE occurrence during follow-up, patients were categorized into MACE (n = 66) and non-MACE (n = 130) groups. Baseline characteristics, comorbidities, and laboratory parameters were collected. Logistic regression analysis was utilized to assess independent risk factors for MACEs, and their predictive value was evaluated using receiver operating characteristic (ROC) curve analysis.

Results: Over a 21-month follow-up, the cumulative MACE incidence was 33.67%. Multivariate analysis revealed that serum albumin was an independent protective factor for MACEs (OR = 0.679, 95% CI: 0.558–0.827, P < 0.01), whereas C-reactive protein (CRP) was an independent risk factor (OR = 1.151, 95% CI: 0.994–1.334, P = 0.046). ROC curve analysis demonstrated that the combination of serum albumin and CRP provided the best predictive performance, with an area under the curve (AUC) of 0.7224 (sensitivity 81.77%, specificity 51.52%).

Conclusion: Low serum albumin and elevated CRP are independent risk factors for MACEs in MHD patients. The combined assessment of these two biomarkers offers good predictive value for MACEs and may serve as an effective tool for clinical screening of high-risk patients.

Keywords: Maintenance hemodialysis, Major adverse cardiovascular events, Clinical characteristics, Risk factors, End-stage renal disease

Introduction

Patients with end-stage renal disease (ESRD) undergoing maintenance hemodialysis (MHD) face a markedly elevated risk of cardiovascular disease (CVD) and related mortality. Despite continuous advancements in dialysis technology, the long-term survival of MHD patients remains suboptimal.[1] Patients with end-stage renal disease (ESRD) undergoing maintenance hemodialysis (MHD) face a markedly elevated risk of cardiovascular disease (CVD) and related mortality. Despite continuous advancements in dialysis technology, the long-term survival of MHD patients remains suboptimal.[2,3] Among these factors, the malnutrition-inflammation-atherosclerosis (MIA) syndrome has been increasingly recognized as a pivotal pathological link connecting chronic inflammation, nutritional depletion, and accelerated CVD in ESRD.[4,5] Specifically, serum albumin and C-reactive protein (CRP), as readily accessible biomarkers reflecting nutritional status

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and systemic inflammation respectively, have been shown in recent studies to be strongly associated with cardiovascular outcomes and all-cause mortality in dialysis populations.[5] However, the comparative predictive value and potential interaction of these biomarkers with traditional risk factors, such as hypertension and mineral bone disorder parameters, within specific clinical cohorts warrant further investigation to refine risk stratification models.

The pathophysiological mechanisms underlying MACEs in MHD patients are complex. In addition to traditional risk factors like hypertension, diabetes, and dyslipidemia, a spectrum of uremia-specific non-traditional risk factors are involved, such as chronic kidney disease-mineral and bone disorder (CKD-MBD), microinflammatory state, oxidative stress, anemia, volume overload, and uremic toxin accumulation.[2,6–10] These multifaceted factors act synergistically to accelerate the processes of atherosclerosis, vascular calcification, and myocardial fibrosis, resulting in distinct MACE clinical manifestations and risk profiles specific to the MHD population.

Although existing research has extensively explored MACE risk in MHD patients, the relative weight and contribution of various risk factors may differ across populations and healthcare centers. Therefore, a detailed analysis of the clinical characteristics of MACEs in MHD cohort and the systematic identification of independent risk factors hold significant clinical importance for developing precise prevention strategies and improving patient outcomes. This study aims to comprehensively collect baseline data, clinical indicators, and laboratory parameters from MHD patients via a retrospective analysis and utilize a multivariate logistic regression model to identify independent risk factors associated with MACEs. By focusing on readily available clinical biomarkers, including nutritional and inflammatory markers alongside traditional risk factors, this investigation seeks to develop a pragmatic and broadly applicable risk assessment tool. The findings are expected to offer an evidence-based foundation for early risk stratification and individualized intervention in routine clinical practice, potentially improving cardiovascular outcomes in this high-risk population.

Materials and Methods

Subjects

The present study was designed to be a single-center, retrospective cohort investigation. To explore the association between baseline metabolic indicators and major adverse cardiovascular events (MACEs) in patients undergoing maintenance hemodialysis (MHD), we consecutively enrolled all eligible patients who received regular MHD (dialysis duration $\geq$ 6 months) at the Blood Purification Center of the Department of Nephrology at our hospital between January 2021 and August 2022. A total of 196 patients met the inclusion criteria and constituted the final study cohort. Based on follow-up data through July 31, 2024, the cohort was stratified into two groups for the primary analysis: those who experienced MACEs (n = 66) and those who did not (n = 130). The sample size was determined by the available retrospective data during the study period. For the planned multivariable logistic regression analysis, we ensured that the number of events (MACEs = 66) was sufficient, adhering to the common guideline of having at least 10 events per predictor variable considered in the model. Ethical approval for the study protocol was granted by the Ethics Committee of The Second Affiliated Hospital of Soochow University (No. JD-LK2024062-I01). Since this study was a retrospective design involving only the analysis of anonymized clinical data without additional intervention or sample collection, posing minimal risk to patients, and obtaining informed consent from all participants was impracticable, the Ethics Committee waived the requirement for informed consent. All patient data were handled in accordance with the principles of the Declaration of Helsinki, ensuring data confidentiality.

Inclusion Criteria

(1) Aged $\geq$ 18 years; (2) Regular MHD treatment (three sessions per week, four hours per session) with a dialysis duration of $\geq$ 6 months; (3) Availability of complete baseline clinical data, including demographic information, key comorbidities (hypertension, diabetes, hyperlipidemia, hyperphosphatemia), and records of laboratory parameters of interest in this study (serum albumin, C-reactive protein [CRP], prealbumin).

Exclusion Criteria

(1) Severe liver disease or chronic infectious diseases; (2) Patients with high bleeding risk; (3) Patients with mental disorders; (4) History of cardiac valve replacement or congenital heart disease; (5) Incomplete clinical data or loss to follow-up.

Treatment Protocols

MHD: Dialysis procedures for all enrolled patients adhered to the Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines.[11] All patients received a standard MHD regimen with a frequency of three four-hour sessions/week. Dialysis was administered with blood and dialysate flow rates set at 200–250 mL/min and 500 mL/min, respectively. Vascular access was established via autogenous arteriovenous fistula or tunneled jugular dialysis catheter.

Adjunctive therapy: Both groups received conventional baseline management in accordance with standard clinical care protocols, including blood glucose and pressure control, correction of acid-base imbalances, and dietary guidance recommending a low-salt, low-potassium, low-phosphorus, high-quality protein diet to reduce renal metabolic load.

Data Collection

Baseline patient data were collected through the electronic medical record system, including demographic information [sex, age, body mass index (BMI)], clinical data (smoking history, alcohol history, disease duration, dialysis vintage), comorbidities (diabetes, hyperlipidemia, hyperphosphatemia, hypertension), and laboratory parameters (prealbumin, serum albumin, CRP). Laboratory parameters were based on the first recorded values obtained after patients had achieved stable dialysis status (typically one month after initiating regular dialysis), during the enrollment period from January 2021 to August 2022. The selection of these indicators was based on their routine clinical availability and substantial evidence in the literature supporting their strong association with clinical outcomes in maintenance hemodialysis (MHD) patients. Specifically, markers reflecting nutritional status (serum albumin, prealbumin) and micro-inflammatory status (C-reactive protein, CRP) are core components of the malnutrition-inflammation-atherosclerosis (MIA) syndrome. While we recognize the importance of other biomarkers such as NT-proBNP and cardiac troponin I/T, these were not included in the analysis due to the retrospective nature of this study and the high rate of missing data resulting from inconsistent routine screening for these markers across all MHD patients in our center.

Follow-Up and Endpoint Definition

Data collection for endpoint ascertainment was primarily achieved by retrospective review of the electronic medical record (EMR) system up to the study cutoff date (July 31, 2024). To minimize missing data and clarify ambiguous records, research personnel attempted to contact patients or their families by telephone when necessary. This contact was solely for the purpose of verifying clinical events or survival status documented in or missing from the EMR, not as part of a prospective intervention. Similarly, information from any outpatient visits that occurred within the study period was extracted from the EMR. Patients were considered to have incomplete data (not "lost to follow-up" in a prospective sense) if, after two consecutive telephone attempts, their endpoint status (especially for non-fatal events or cause of death) could not be verified, or if they explicitly declined to provide verification. The primary endpoint, MACEs (up to July 31, 2024), was defined as a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or severe coronary artery disease (CAD) requiring revascularization.

To ensure accurate endpoint adjudication, a defined confirmation process and criteria were established: (1) Cardiovascular Death: Adjudication was based on a synthesis of: a) the underlying cause of death listed on the official death certificate; b) clinical circumstances documented in hospital records, progress notes, and discharge summaries around the time of death; c) supplementary information regarding the circumstances of death obtained from family members via telephone (eg, occurrence during dialysis, at home, witnessed symptoms). For cases of sudden death, in the absence of clear evidence for a non-cardiovascular cause (eg, active infection, trauma), they were adjudicated as cardiovascular by the Endpoint Committee based on the epidemiological profile and clinical consensus in this population; (2) Non-Cardiovascular Death: Deaths occurring during the study period with clear evidence supporting a non-cardiovascular cause (eg, terminal infection [sepsis], advanced malignancy, respiratory failure, major hemorrhage) were recorded as "non-cardiovascular death." These cases were not counted toward the primary endpoint but were considered in analyses of all-cause mortality; (3) non-fatal myocardial infarction diagnosis relied on hospitalization records, progress notes, electrocardiograms, and dynamic changes in cardiac biomarkers (primarily troponin); (4) non-fatal stroke required neurologist consultation notes, hospital records, and supporting head CT or MRI reports; (5) severe

CAD requiring revascularization necessitated corresponding coronary angiography reports and procedure records (percutaneous coronary intervention or coronary artery bypass grafting).[12–14] To ensure objectivity and consistency in endpoint determination, an independent Endpoint Adjudication Committee was established, comprising one cardiovascular specialist, one neurologist, and one nephrologist, all blinded to patient group assignment. During adjudication, the committee reviewed anonymized copies of all relevant source documents and made independent judgments based on prespecified criteria. Discrepancies were resolved through consensus discussion.

Statistical Analysis

Data analysis was conducted applying GraphPad Prism (version 8.0.2) and IBM SPSS Statistics (version 27). Continuous variables following a normal distribution were presented as mean ± standard deviation ($\overline{x} \pm s$) and compared with independent samples *t*-tests, while non-normally distributed continuous data were reported as median with interquartile range (IQR) and analyzed by the Mann–Whitney *U*-test. Categorical variables were summarized as counts (percentages) and compared employing either the χ^2-test or Fisher's exact test (if expected frequencies were < 5). To identify independent risk factors for MACEs in the MHD population, univariate analysis was first performed. Given the limited sample size, and to develop a parsimonious yet robust multivariate model, we predetermined the inclusion of clinically relevant factors such as age, sex, and dialysis duration into the multivariate adjustment, regardless of their statistical significance in univariate analysis. Additionally, variables with a significance level of $P<0.05$ in univariate analysis were incorporated into the multivariate binary logistic regression model to calculate odds ratios (OR) with their corresponding 95% confidence intervals (95% CI). Multicollinearity among the included variables was assessed via variance inflation factor (VIF) calculations, and all variables had VIF values below 5, indicating that collinearity did not compromise model stability or interpretation. To further verify model stability and the reliability of OR estimates, an internal validation was carried out by the Bootstrap resampling technique, specifically set to 1,000 resamples with a sample size equal to the original dataset (n = 196). Logistic regression models were refitted within each Bootstrap sample, and Bootstrap CIs for the ORs were calculated using the percentile method based on the 1,000 results. Additionally, the predictive performance of significant indicators for MACEs was evaluated by constructing receiver operating characteristic (ROC) curves. The area under the curve (AUC), along with sensitivity and specificity, was calculated to quantify discriminatory power, and optimal cut-off values were determined. A two-sided *P*-value of less than 0.05 was considered statistically significant for all tests.

Results

MACE Incidence in MHD Patients

Among the 196 MHD patients, the median follow-up duration was 21 months (range: 12–30 months), with 66 patients (33.67%) experiencing MACEs during the follow-up period. The distribution of specific MACE components is shown in Table 1. Cardiovascular death was the most frequent event, occurring in 29 patients, accounting for 43.94% of all MACEs, corresponding to an incidence of 14.8% in the total study population. Non-fatal myocardial infarction and severe CAD requiring revascularization occurred with equal frequency (14 cases each), each constituting 21.21% of MACEs, with an incidence of 7.14% in the total population. Non-fatal stroke had a relatively lower incidence, with 9 cases, accounting for 13.64% of MACEs and 4.59% of the total population. A total of five patients were lost to follow-up, resulting in a loss-to-follow-up rate of 2.55%. Additionally, 15 patients died due to non-cardiovascular causes, primarily including infection (n=7), malignancy (n=4), gastrointestinal bleeding (n=2), and other reasons (n=2). These events were not included as part of the primary endpoint. In summary, the overall incidence of MACEs in MHD patients was high (approximately one-third), with cardiovascular death being the predominant clinical manifestation.

Univariate Analysis of Potential Risk Factors for MACEs

According to the univariate analysis results (Table 2), we systematically compared the clinical characteristics of MHD patients who experienced MACEs (MACE group, n = 66) versus those who did not (non-MACE group, n = 130) to preliminarily screen for potential risk factors. The results revealed significant differences between the two groups across

Table 1 Distribution of MACEs in MHD Patients (n = 196)

Event Type	n	Proportion within MACEs (%)	Proportion in Total population (%)
Total MACEs	66	100.0	33.67
Cardiovascular death	29	43.94	14.8
Non-fatal myocardial infarction	14	21.21	7.14
Non-fatal stroke	9	13.64	4.59
Severe CAD requiring revascularization	14	21.21	7.14
Loss to follow-up	5	N/A	2.55
Non-cardiovascular death	15	N/A	7

Abbreviations: MACEs, Major adverse cardiovascular events; MHD, Maintenance hemodialysis; CAD, Coronary artery disease; N/A, Not applicable.

Table 2 Univariate Analysis of Potential Risk Factors for MACEs in MHD Patients

Clinical Characteristic	MACE Group (n = 66)	Non-MACE Group (n = 130)	F/χ^2	*P*
Age (years)	54 (51.75, 55)	54 (52, 57)	1.125	0.262
Sex (male/female)	45/21	88/42	0.069	0.945
BMI (kg/m^2)	22.66 ± 1.20	22.44 ± 1.05	0.094	0.926
Smoking history (yes/no)	39/27	79/51	0.227	0.821
Alcohol history (yes/no)	44/22	82/48	0.496	0.620
Disease duration (years)	2.59 ± 0.27	2.62 ± 0.29	1.806	0.072
Dialysis vintage (months)	9 (7, 10.25)	8 (7, 9)	1.037	0.301
Diabetes [n (%)]	10 (15.15%)	11 (8.46%)	1.431	0.152
Hyperlipidemia [n (%)]	20 (30.30%)	20 (15.38%)	2.449	0.014
Hyperphosphatemia [n (%)]	23 (34.85%)	27 (20.77%)	2.137	0.033
Hypertension [n (%)]	29 (43.94%)	38 (29.23%)	2.052	0.040
Serum albumin (g/L)	31.55 (30.18, 33.33)	33.1 (31.50, 34.80)	4.121	< 0.001
CRP (mg/L)	20.55 (17.28, 22.88)	19.5 (17.38, 20.63)	2.635	0.009
Prealbumin (mg/L)	114.88 ± 28.40	130.35 ± 31.27	2.774	0.006

Abbreviations: MACEs, Major adverse cardiovascular events; MHD, Maintenance hemodialysis; BMI, Body mass index; CRP, C-reactive protein.

several clinical indicators. Regarding comorbidities, the MACE group had significantly higher rates of hyperlipidemia (30.30% vs 15.38%, $P = 0.0143$), hyperphosphatemia (34.85% vs 20.77%, $P = 0.0326$), and hypertension (43.94% vs 29.23%, $P = 0.0402$) relative to the non-MACE group. A higher numerical prevalence of diabetes in the MACE group (15.15% vs 8.46%) was not associated with a statistically significant intergroup difference ($P = 0.1524$). Concerning laboratory parameters, the MACE group exhibited a markedly poorer nutritional and inflammatory status, characterized by lower serum albumin levels, higher CRP levels, and significantly reduced prealbumin levels (all $P < 0.05$). However, the groups did not differ significantly regarding age, sex, BMI, smoking or alcohol history, disease duration, and dialysis vintage (all $P > 0.05$). In conclusion, univariate analysis preliminarily suggested associations between hyperlipidemia, hyperphosphatemia, hypertension, low serum albumin, high CRP, and low prealbumin levels with MACEs in MHD patients. These variables were therefore included in the subsequent multivariate logistic regression analysis to further assess their independent effects.

Multivariate Binary Logistic Regression Identifying Independent Risk Factors for MACEs

In addition to variables with $P < 0.05$ in the univariate analysis, all pre-specified baseline variables of established clinical importance (such as age, sex, and dialysis duration) were forced into the multivariate binary logistic regression model.

Table 3 Multivariate Binary Logistic Regression Identifying Independent Risk Factors for MACEs in MHD Patients

Variable	β	SE	Wald	*P*-value	OR	95% CI (Lower, Upper)
Constant	-	4.985	8.360	0.04	-	-
Prealbumin	0.206	0.705	0.085	0.770	1.229	0.309–4.893
Hyperlipidemia	−0.827	0.471	3.084	0.079	0.437	0.147–2.013
Hyperphosphatemia	−0.240	0.479	0.250	0.617	0.787	0.0.307–1.101
Hypertension	−0.351	0.397	0.779	0.378	0.704	0.323–1.534
Serum albumin (g/L)	−0.387	0.100	14.859	< 0.01	0.679	0.558–0.827
CRP (mg/L)	0.141	0.075	3.527	0.046	1.151	0.994–1.334
Age (years)	−0.067	0.059	1.284	0.257	0.935	0.833–1.050
Sex (male/female)	−0.246	0.381	0.416	0.519	0.782	0.370–1.651
Disease duration (years)	−0.654	0.495	1.748	0.186	0.520	0.197–1.371
Dialysis vintage (months)	0.085	0.094	0.822	0.365	1.089	0.906–1.310

Abbreviations: MACEs, Major adverse cardiovascular events; MHD, Maintenance hemodialysis; CRP, C-reactive protein; SE, Standard error; OR, Odds ratio; CI, Confidence interval.

The results of the multivariate binary logistic regression analysis (Table 3) indicated that serum albumin and C-reactive protein were independent factors influencing MACEs. Specifically, serum albumin emerged as an independent protective factor (OR = 0.679, 95% CI: 0.558–0.827, P < 0.01), meaning that for every 1 g/L increase in serum albumin, the risk of MACEs decreased by approximately 32.1%. Conversely, CRP was identified as an independent risk factor (OR = 1.151, 95% CI: 0.994–1.334, P = 0.046), suggesting that every 1 mg/L increase in CRP was associated with a 15.1% increase in MACE risk. Furthermore, prealbumin, hyperlipidemia, hyperphosphatemia, hypertension, age, sex, disease duration, and dialysis vintage did not demonstrate independent associations with MACEs in this model (all P > 0.05).

ROC Analysis Evaluating the Diagnostic Value of Independent Risk Factors for Predicting MACEs

ROC analysis evaluating the diagnostic value of serum albumin, CRP, and their combination for predicting MACEs in MHD patients (Table 4, Figure 1) revealed that serum albumin alone had an AUC of 0.6699 (95% CI: 0.5889–0.7509), implying modest predictive ability. At its optimal cut-off value, sensitivity was high (80.77%), but specificity was relatively low (42.42%). CRP alone demonstrated weak predictive power, with an AUC of only 0.5741 (95% CI: 0.4813–0.6669; sensitivity 70.77%; specificity 46.97%), suggesting limited diagnostic value. However, the combination of serum albumin and CRP significantly enhanced predictive performance, increasing the AUC to 0.7224 (95% CI: 0.6458–0.7989). This combined model maintained high sensitivity (80.77%) while improving specificity to 51.52%. In summary, although serum albumin and CRP individually offered limited predictive value, their combined model demonstrated superior, moderate-level predictive performance, effectively identifying MHD patients at risk for MACEs with high sensitivity.

Table 4 ROC Curve Analysis Evaluating the Diagnostic Value of Independent Risk Factors for MACEs in MHD Patients

Indicator	AUC	Sensitivity (%)	Specificity (%)	Optimal cut-off	95% CI
Serum albumin (g/L)	0.6699	80.77%	42.42%	0.2319	0.5889–0.7509
CRP (mg/L)	0.5741	70.77%	46.97%	0.1774	0.4813–0.6669
Combined analysis	0.7224	80.77	51.52%	0.3229	0.6458–0.7989

Abbreviations: ROC, Receiver operating characteristic; MACEs, Major adverse cardiovascular events; MHD, Maintenance hemodialysis; CRP, C-reactive protein; AUC, Area under the curve; CI, Confidence interval.

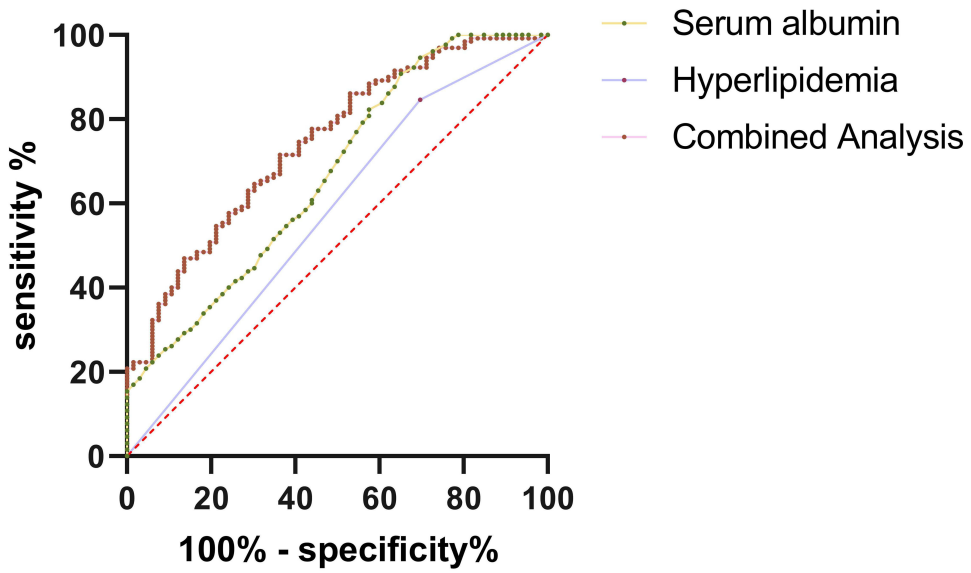

Figure 1 ROC curve analysis evaluating the diagnostic value of independent risk factors for MACEs in MHD patients.
Abbreviations: ROC, Receiver operating characteristic; MACEs, Major adverse cardiovascular events; MHD, Maintenance hemodialysis; CRP, C-reactive protein.

Discussion

This study, through a systematic analysis of clinical data from 196 MHD patients, thoroughly investigated the risk factors and predictive value for MACEs. Our research revealed a key finding that after adjusting for multiple confounding factors, serum albumin and CRP were independent factors influencing MACE occurrence in MHD patients. It is noteworthy that traditional risk factors such as hypertension and hyperphosphatemia did not retain independent predictive value in the model when nutritional and inflammatory markers were included. This may be partly attributable to methodological differences (the former were analyzed as categorical variables, while the latter as continuous variables), and may also reflect the unique pathophysiological context in MHD patients, such as the "reverse epidemiology" phenomenon of blood pressure, as well as the possibility that these conventional factors may indirectly influence cardiovascular risk partially through their effects on nutritional and inflammatory status. This finding provides a fresh perspective on understanding the unique pathophysiological mechanisms of cardiovascular diseases in MHD patients and carries significant implications for risk assessment strategies in clinical practice.

During a median follow-up of 21 months, the cumulative incidence of major adverse cardiovascular events (MACEs) was 33.67%, which is significantly higher than that observed in the general population and in most coronary artery disease cohorts. This finding reaffirms the persistently high burden of cardiovascular disease as a leading cause of morbidity and mortality in MHD patients.[15] The distribution of event types showed that cardiovascular death was the most common, followed by non-fatal myocardial infarction and severe coronary artery disease requiring revascularization, suggesting that atherosclerotic events constitute a central pathological process influencing outcomes in this population. This aligns with previous studies: Gajashree M et al noted that atherosclerotic cardiovascular disease was a primary contributor to mortality in the ESRD population, and its risk scores might serve as effective tools for assessing arteriovenous fistula failure and prognosis in MHD patients; Girish Vasudeo Kumthekar et al similarly emphasized the dominant role of atherosclerotic cardiovascular disease in mortality and complications among MHD patients.[16–18]

The most significant finding of this study is establishing the central role of serum albumin and CRP in cardiovascular risk assessment for MHD patients. Multivariate analysis determined serum albumin as an independent protective factor against MACEs, suggesting that each 1 g/L increase in serum albumin level was linked to an approximately 30.8% reduction in MACE risk. This finding strongly supports the "malnutrition–inflammation–atherosclerosis (MIA) syndrome" theory, which has been progressively proposed since the early 21st century and posits that malnutrition, chronic micro-inflammatory status, and their interplay with atherosclerosis constitute central mechanisms underlying cardiovascular risk in dialysis patients.[19–21] In MHD patients, hypoalbuminemia not only reflects inadequate protein intake but also

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signifies a systemic inflammatory response, contributing to MACE development through multiple pathways such as promoting muscle wasting, endothelial dysfunction, and accelerated atherosclerosis. Our results are consistent with the conclusions of Pierre Laurent et al, confirming that hypoalbuminemia is a strong predictor of death in MHD patients, potentially surpassing many traditional risk factors in predictive value.[22,23] Concurrently, CRP as an independent risk factor also demonstrated significant predictive value. This finding echoes the research by Shen Jinwei et al, whose study suggested that a microinflammatory state could exacerbate malnutrition in MHD patients and serve as a strong predictor of all-cause and cardiovascular mortality.[24] Our study further validated that CRP retained its independent predictive power even after adjusting for traditional risk factors, highlighting the central role of the inflammatory pathway in uremia-related cardiovascular pathology. Furthermore, Notably, traditional risk factors such as hypertension and hyperphosphatemia were significant in univariate analysis but lost their independent predictive value after adjustment for albumin and CRP. This observation may be influenced not only by the form of variable inclusion (categorical versus continuous) and its impact on model sensitivity, but also suggests that these factors may partly affect cardiovascular risk indirectly through their influence on nutritional and inflammatory status. Furthermore, it underscores the distinct pathophysiological mechanisms of cardiovascular disease in MHD patients, such as the "reverse epidemiology" phenomenon observed in blood pressure management, which warrants consideration. Additionally, this study evaluated the predictive value of serum albumin and CRP for MACEs in MHD patients using ROC curve analysis. The results showed that serum albumin alone possessed modest predictive ability (AUC = 0.6699) but had high sensitivity (80.77%), indicating its effectiveness as a nutritional status indicator in initial screening for identifying most high-risk patients. The predictive efficacy of CRP alone was modest (AUC = 0.5741), indicating limitations in using a single inflammatory marker for risk assessment. Notably, the predictive model combining serum albumin and CRP demonstrated improved discriminative ability, with the AUC increasing to 0.7224. This enhancement carries important pathophysiological implications and further supports the theoretical framework of the malnutrition–inflammation–atherosclerosis (MIA) syndrome. Albumin primarily reflects nutritional reserves and protein metabolic status, while CRP represents the level of persistent microinflammation. They illuminate different dimensions of the specific pathological background of cardiovascular risk in MHD patients. Their synergistic effect indicates that a combined assessment can more comprehensively capture the patient's overall pathophysiological state, thereby improving the accuracy of risk identification. In terms of clinical translation, this combined model shows significant application potential. The indicators it relies on are routinely tested, facilitating implementation in clinical practice without adding extra healthcare costs. Moreover, the model maintains high sensitivity (80.77%) while improving specificity to 51.52%. In screening scenarios, high sensitivity is crucial for minimizing missed diagnoses and early identification of high-risk patients requiring intensified intervention. Therefore, this combined model holds promise as an effective tool for cardiovascular risk stratification and early warning in MHD patients.

Limitations and Future Perspectives

Several limitations of our study warrant careful consideration. First, the constrained sample size (total n = 196) may affect statistical power, particularly in multivariate analyses. Although we enhanced result stability using the Bootstrap method, validation in larger samples remains necessary. Second, the single-center design limits the generalizability of the findings, as patient characteristics and treatment practices may vary across different regions and dialysis centers. Third, regarding indicator measurements, we relied on single-time-point laboratory data, which may not reflect dynamic trends in biomarkers; time-weighted averages might provide a more accurate risk asse ssment. Fourth, this study did not comprehensively collect and analyze medication usage, such as phosphate binders, statins, and erythropoietin, which could significantly influence cardiovascular risk and represent important uncontrolled confounding factors. Fifth, the lack of data on other emerging biomarkers, such as fibroblast growth factor-23 and lipoprotein(a), restricts a more comprehensive understanding of the mechanisms underlying uremia-related cardiovascular pathology. Sixth, due to the retrospective nature of the study, we were unable to obtain complete cardiovascular history (eg, coronary artery disease, myocardial infarction, heart failure, history of stroke/TIA, or prior PCI/CABG) and cardiac function parameters (eg, left ventricular ejection fraction) for all patients. These are strong predictors of MACEs in MHD patients, and failure to adjust for them may lead to residual confounding and affect the robustness of the "independent risk factor" conclusions. We acknowledge this as a significant limitation and advise caution in interpreting the results (ie, that serum albumin

and CRP are "independent" factors). Future studies should endeavor to collect these key covariates. Seventh, although we noted the importance of pre- and post-dialysis parameter changes, we were unable to deeply explore the potential impact of dialysis adequacy (eg, Kt/V) on cardiovascular risk. Eighth, the sample size calculation was based on an effect size for detecting group differences in continuous variables (eg, CRP, albumin), whereas the primary analysis was a multivariate logistic regression for a binary outcome (MACEs); the two do not perfectly align. Finally, unequal follow-up times may introduce bias. Although logistic regression is appropriate in the context of assessing a binary outcome at a fixed endpoint, future studies using time-to-event analysis methods (eg, Cox proportional hazards model) that account for the time factor may be more ideal.

Future research should focus on directions as follows: First, conduct multicenter, large-scale prospective cohort studies to validate the generalizability of the current findings and establish more precise risk prediction models, paying particular attention to performance variations across different patient subgroups. Second, perform dynamic monitoring studies to investigate the association between biomarker trajectories over time and MACEs, which may yield more sensitive predictive indicators. Third, undertake in-depth mechanistic studies to explore the causal pathways linking nutritional status, microinflammation, and cardiovascular pathology at the molecular level, providing a theoretical basis for targeted therapies. Fourth, promote interventional studies assessing whether improving nutritional status and controlling microinflammation can effectively reduce MACE incidence, which is the crucial step for validating our hypothesis. Finally, develop individualized prediction tools integrating multi-omics data, incorporating emerging technologies like genomics and proteomics, to achieve more precise risk stratification.

Conclusion

This study, through systematic analysis, confirms that low serum albumin and elevated CRP are significant and independent risk factors for MACEs in the MHD population in our cohort. In our specific analytical model, which adjusted for available data on traditional factors (categorized as present/absent), these nutritional and inflammatory markers provided significant independent predictive value. This finding highlights the critical importance of integrating assessments of nutritional status and microinflammation into the cardiovascular risk evaluation of MHD patients, alongside the management of established traditional risk factors. The combined prediction model based on serum albumin and CRP demonstrates good discriminatory ability, and its high sensitivity supports its potential utility as a component of a broader clinical screening strategy. The application of this model, in conjunction with other key clinical parameters, could enhance risk stratification and inform individualized intervention plans.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

Ethical approval for the study protocol was granted by the Ethics Committee of The Second Affiliated Hospital of Soochow University (No. JD-LK2024062-I01), with a waiver of informed consent.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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