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Circulating RIPK3 level predicts all-cause mortality in patients on maintenance hemodialysis: a 4-year prospective cohort study

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Abstract

Background Maintenance hemodialysis (MHD) is a well-established modality of renal replacement treatment for patients with end-stage renal disease. Currently, receptor-interacting protein kinase-3 (RIPK3) is considered as a key regulator of inflammation. But its association with mortality in MHD patients remains unclear. Thus, the aim of the present study was to observe the predictive value of plasma RIPK3 for all-cause mortality in patients undergoing MHD with a 4-year follow-up.

Methods 148 patients undergoing MHD treatment during June 2020 were enrolled. The plasma RIPK3 levels were measured via enzyme-linked immunosorbent assay. Patients were followed up for 4 years to record all-cause mortality until June 2024.

Results During the 4-year follow-up period, the total incidence of all-cause mortality was 34.46% (51 of 148 participants). Compared with the survival group, the non-survival group presented significantly greater age, diabetes prevalence, serum hs-CRP, plasma RIPK3, and lower serum albumin levels. Cox multivariate analysis revealed an independent association between plasma RIPK3 levels and all-cause mortality. The optimal cutoff value to predict all-cause mortality in patients receiving MHD was 251.54 ng/mL with the AUC of 0.7 (95% CI 0.61–0.79). Kaplan-Meier estimates showed a significantly greater overall survival probability for patients with RIPK3 concentrations lower than 251.5 ng/mL than for those with RIPK3 concentrations ≥ 251.5 ng/mL ($p < 0.001$).

Conclusion Plasma RIPK3 level may serve as an independent predictor for all-cause mortality in MHD patients.

Keywords End-stage renal disease, Maintenance hemodialysis, RIPK3, All-cause mortality

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Introduction

Chronic kidney disease (CKD) has emerged as a global health burden [1–2]. Its most severe form is end-stage renal disease (ESRD), which requires renal replacement treatment (RRT). Maintenance hemodialysis (MHD) is a well-established modality of RRT for ESRD patients [3]. However, numerous studies have reported high mortality among patients receiving MHD [4–5]. Thus, the importance of identifying mortality biomarkers in this population has become evident. Previously, studies revealed an association between this elevated risk and several factors, including diabetes, inflammation, malnutrition, frailty, and uremia-related elements unique to ESRD [6–11].

Cell death plays a role in the pathogenesis of organ dysfunction, contributing to all-cause mortality in inflammatory conditions and various diseases [12–13]. Recently, the understanding of cell death has expanded to include forms of programmed necrosis, which not only cause local organ injury but also release proinflammatory endogenous danger signals [13–14]. Receptor-interacting protein kinase-3 (RIPK3) is currently considered as a key regulator of programmed necrosis [15–16]. Previous studies have revealed the role of elevated circulating RIPK3 levels as a biomarker for the diagnosis and prognosis of several diseases, including sepsis, acute lung injury, coronary artery disease, heart failure and brain injury [11, 17–20]. However, there is limited clinical evidence regarding the association between circulating RIPK3 and mortality in MHD patients.

Therefore, the aim of the present study was to observe the predictive value of plasma RIPK3 for all-cause mortality in patients undergoing MHD with a 4-year follow-up.

Methods

Ethical approval

This study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Southeast University Zhongda Hospital (2019ZDSYLL110-P01). The informed consent was obtained from all participants.

Study population and design

This study was conducted in the dialysis center of Zhongda Hospital Affiliated to Southeast University, Nanjing. Patients on MHD with stable dialysis time > 3 months thrice per week for 4 h each session during June 2020, and those who were willing to participate in were enrolled. Exclusion criteria included age under 18, or a history of malignant disease, or diagnosed with active liver disease, or with a cardiac or cerebrovascular event during the past 3 months, or with missing data on variables of interest.

Clinical data collection and laboratory measurements

The general clinical data of the patients were collected, including age, sex, concomitant disease (diabetes, hypertension). Predialysis venous blood samples were collected. Hemoglobin (Hb), ferritin, serum calcium (Ca), serum phosphorous (p), albumin, parathyroid hormone (PTH), and high-sensitivity C-reactive protein (hs-CRP) were measured using routine laboratory methods. The plasma RIPK3 levels were measured by a commercially available enzyme-linked immunosorbent assay kit (CSB-EL019737HU, CUSABIO) following the manufacturer's instructions.

Follow-up

All subjects were followed up after baseline assessments until death or to the end of the follow-up in this study. All-cause mortality until 4-year after inclusion was used as an end point.

Statistical analysis

The statistical power of sample size calculation was 0.8 (β was set to 0.2). Statistical analyses were performed using SPSS (version 25.0, IBM Corp., Armonk, NY) and R (version 4.3.0, R Development Core Team) software. The data are expressed as counts and percentages for categorical variables, mean ± standard deviation (SD) or median and interquartile range for continuous variables in the table, and mean ± standard error of the mean (SEM) for the graphical data. The unpaired *t*-test or Mann–Whitney test was used to compare two groups. One-way ANOVA was used to compare three groups. The Cox regression model was used to analyze the risk factors for all-cause death in patients with MHD. Pearson's correlation coefficient test was performed to assess the independent factor associated with plasma RIPK3 level. The receiver operating characteristic (ROC) curve was used to analyze the predictive ability of RIPK3 on the risk of all-cause death. The area under the curve (AUC) and 95% CI were calculated. The optimal cutoff value for RIPK3 was ascertained using maximally selected rank statistics. Kaplan–Meier survival curves and log-rank tests were used to compare differences in survival rates. All statistical tests were two-tailed, and a P-value of less than 0.05 was considered indicative of statistical significance.

Results

Characteristics of the studied participants at baseline

A total of 148 patients undergoing MHD were included in this study (Fig. 1). The baseline characteristics of these participants are presented in Table 1. The mean age of the patients was 60.07 ± 15.48 years, and 57.43% were male. The prevalence rates of diabetes and hypertension were 31.76% and 91.22%, respectively. During the 4-year follow-up period, the total incidence of all-cause

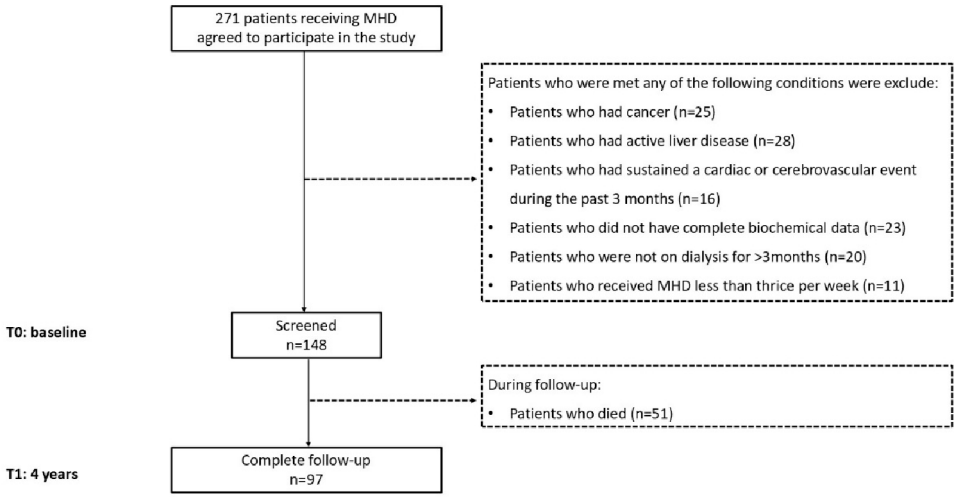

Fig. 1 Flowchart of participants included in the study

Table 1 Baseline characteristics of the study population in survival group and non-survival group

Factors	All patients (n=148)	Survival group (n=97)	Non-survival group (n=51)	*p* value
Age (years)	60.07 ± 15.48	54.63 ± 13.87	70.41 ± 12.97	<0.01
Male gender, n (%)	85 (57.43)	60 (61.86)	25 (49.02)	0.13
Diabetes mellitus, n (%)	47 (31.76)	24 (24.74)	23 (45.10)	0.01
Hypertension, n (%)	135 (91.22)	87 (89.69)	48 (94.12)	0.55
Hemoglobin (g/L)	107.78 ± 19.94	109.65 ± 19.63	104.24 ± 20.23	0.12
Albumin (g/L)	39.27 ± 5.64	40.58 ± 5.58	36.78 ± 4.92	<0.01
Calcium (mmol/L)	2.25 (2.11, 2.42)	2.28 (2.15, 2.46)	2.19 (2.04, 2.34)	0.01
Phosphate (mmol/L)	1.80 ± 0.59	1.88 ± 0.56	1.65 ± 0.62	0.03
Parathyroid hormone (pg/mL)	270.65 (145.12, 563.50)	299.20 (145.50, 578.50)	269.10 (143.75, 453.10)	0.56
Serum ferritin (μg/L)	126.07 (62.62, 271.20)	136.75 (63.07, 279.38)	117.17 (59.25, 257.10)	0.44
C-reactive protein (mg/L)	1.27 (0.82, 9.91)	0.86 (0.82, 4.96)	6.11 (0.91, 19.03)	<0.01
RIPK3 (ng/mL)	184.95 (95.51, 327.58)	160.96 (79.24, 247.63)	292.62 (136.56, 499.77)	<0.01

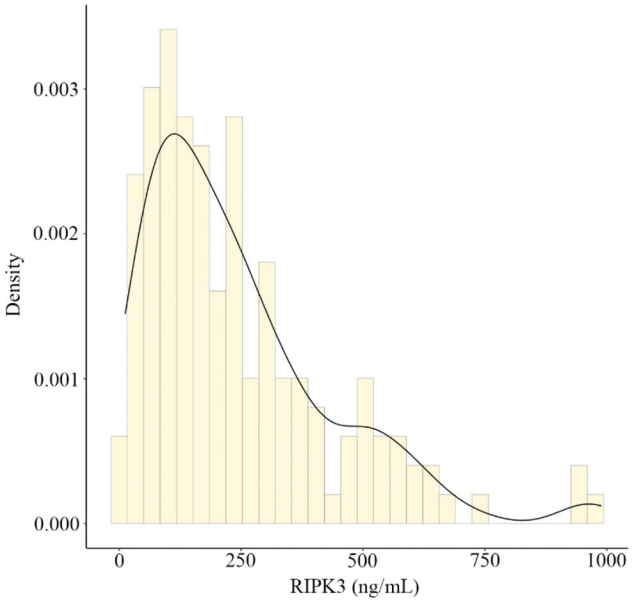

Fig. 2 Histogram of RIPK3 distribution in the study participants

mortality was 34.46% (51 of 148 participants). Causes of death included 18 from cardiovascular disease, 10 from infections, 6 from cerebrovascular accidents, 5 from gastrointestinal hemorrhage, 5 from multiorgan dysfunction, and 7 from unidentified causes. Compared with the survival group, the age, diabetes prevalence, serum hs-CRP and plasma RIPK3 levels were significantly higher in the non-survival group, while serum albumin levels were significantly lower. No significant differences in male sex percentage, hypertension history, Hb, PTH or serum ferritin levels were found between the survival group and the non-survival group.

Parameters between different tertiles of plasma RIPK3 levels

The histogram showed the density of RIPK3 distribution in 148 patients (Fig. 2). According to the tertile of the plasma RIPK3 concentrations, patients were divided into three groups, namely, the low RIPK3 group (RIPK3 < 125.8 ng/mL, $n = 49$), middle RIPK3 group (RIPK3 125.8-266.5 ng/mL, $n = 50$), and high RIPK3

Table 2 Baseline characteristics of the study population stratified by terciles of plasma RIPK3 levels

Factors	RIPK3 in tertiles		
	Low (n=49)	Middle (n=50)	High (n=49)
Age (years)	54.65 ± 15.32	59.28 ± 14.88	66.29 ± 14.24*
Male gender, n (%)	38 (77.55)	28 (56.00) *	19 (38.78) *
Diabetes mellitus, n (%)	11 (22.45)	13 (26.00)	23 (46.94) *#
Hypertension, n (%)	44 (89.80)	45 (90.00)	46 (93.88)
Hemoglobin (g/L)	108.37 ± 18.97	109.62 ± 18.77	105.33 ± 22.09
Albumin (g/L)	40.48 ± 5.76	39.08 ± 5.22	38.26 ± 5.83
Calcium (mmol/L)	2.31 (2.12, 2.46)	2.24 (2.12, 2.46)	2.22 (2.04, 2.34)
Phosphate (mmol/L)	1.98 ± 0.55	1.80 ± 0.57	1.62 ± 0.61*
Parathyroid hormone (pg/mL)	358.50 (176.70, 663.40)	314.60 (157.30, 573.50)	220.90 (91.70, 421.80)
Serum ferritin (μg/L)	110.10 (74.43, 253.33)	135.75 (51.35, 267.42)	140.05 (63.07, 350.25)
C-reactive protein (mg/L)	0.86 (0.82, 4.18)	1.05 (0.82, 9.81)	5.75 (0.82, 18.20) *

Compared with the low RIPK3 group, *$p < 0.05$; compared with the middle RIPK3 group, #$p < 0.05$

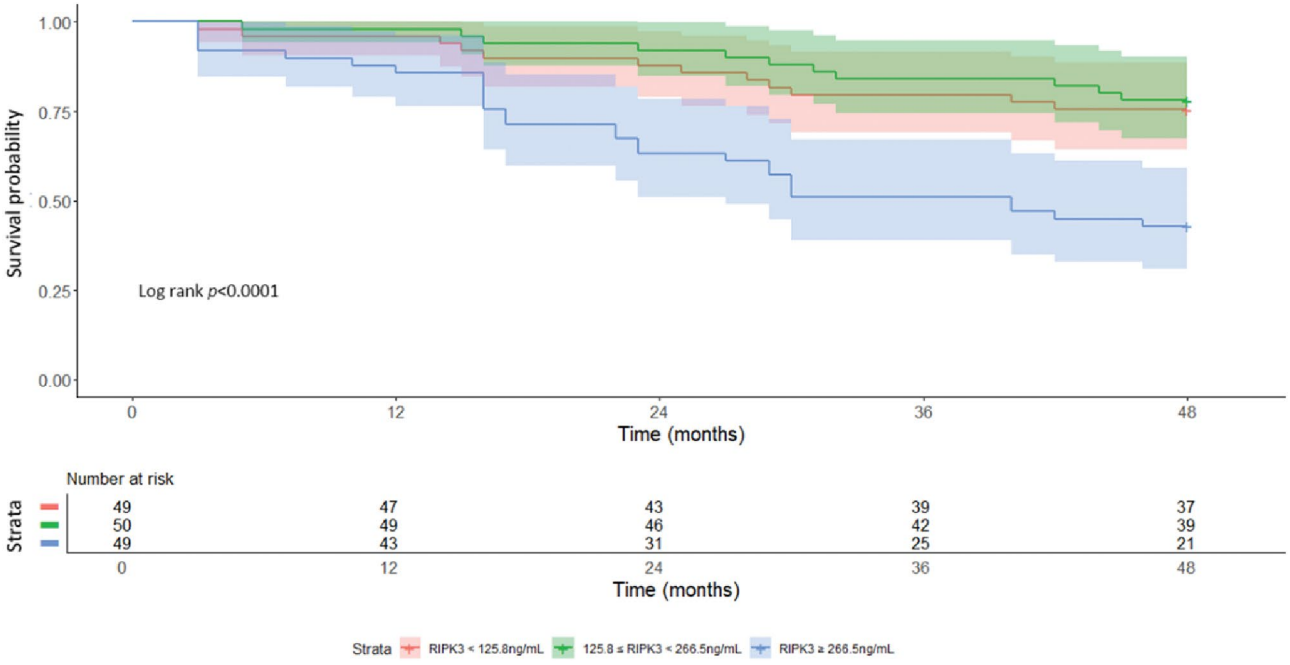

Fig. 3 The Kaplan-Meier estimates of overall survival in MHD patients by plasma RIPK3 terciles

group (RIPK3 > 266.5 ng/mL, $n = 49$). The comparison results of different characteristics between groups are shown in Table 2. Age, male sex percentage, diabetes prevalence and serum hs-CRP were statistically significant ($p < 0.05$). Furthermore, Kaplan-Meier survival analysis revealed a significant difference in all-cause mortality across the three tertiles of plasma RIPK3 levels (Fig. 3).

Relationship between plasma RIPK3 levels and all-cause mortality in MHD patients

As shown in Table 3, Cox multivariate analysis revealed an independent association between plasma RIPK3 levels and all-cause mortality. Each 1 ng/ml increase in RIPK3 was associated with a 1.01-fold greater risk of all-cause mortality ($p = 0.033$). Age ($p < 0.001$) and serum albumin levels ($p = 0.024$) were also independent predictors of all-cause mortality in patients receiving MHD treatment. Further analysis revealed that plasma RIPK3 levels were positively correlated with age ($p < 0.001$, Fig. 4A) and negatively correlated with serum albumin levels ($p = 0.035$).

Predictive ability of serum RIPK3 for all-cause mortality in MHD patients

As shown in Fig. 5, the ROC curve revealed that the AUC of RIPK3 was 0.7 (95% CI 0.61–0.79), with a sensitivity of 77% and a specificity of 61% for predicting all-cause

Table 3 Factors associated with all-cause mortality in MHD patients

Covariate	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95% CI)	*p* value	Hazard Ratio (95% CI)	*p* value
Age (years)	1.07 (1.04-1.09)	<0.001	1.06 (1.03-1.10)	<0.001
Male gender, n (%)	1.49 (0.86-2.59)	0.153	1.69 (0.88-3.24)	0.113
Diabetes mellitus, n (%)	2.17 (1.25-3.77)	0.006	1.54 (0.84-2.81)	0.164
Hypertension, n (%)	1.63 (0.51-5.22)	0.415	1.15 (0.25-5.17)	0.860
Hemoglobin (g/L)	0.99 (0.97-1.00)	0.085	1.00 (0.98-1.02)	0.982
Albumin (g/L)	0.92 (0.89-0.96)	<0.001	0.93 (0.88-0.99)	0.024
Calcium (mmol/L)	0.20 (0.06-0.70)	0.012	0.59 (0.11-3.25)	0.549
Phosphate (mmol/L)	0.59 (0.36-0.98)	0.041	1.58 (0.87-2.87)	0.135
Parathyroid hormone (pg/mL)	1.00 (1.00-1.00)	0.699	1.00 (1.00-1.00)	0.200
Serum ferritin (μg/L)	1.00 (1.00-1.00)	0.528	1.00 (1.00-1.00)	0.876
C-reactive protein (mg/L)	1.00 (1.00-1.01)	0.211	1.00 (0.99-1.01)	0.440
RIPK3 (ng/mL)	1.01 (1.01-1.01)	<0.001	1.01 (1.01-1.01)	0.033

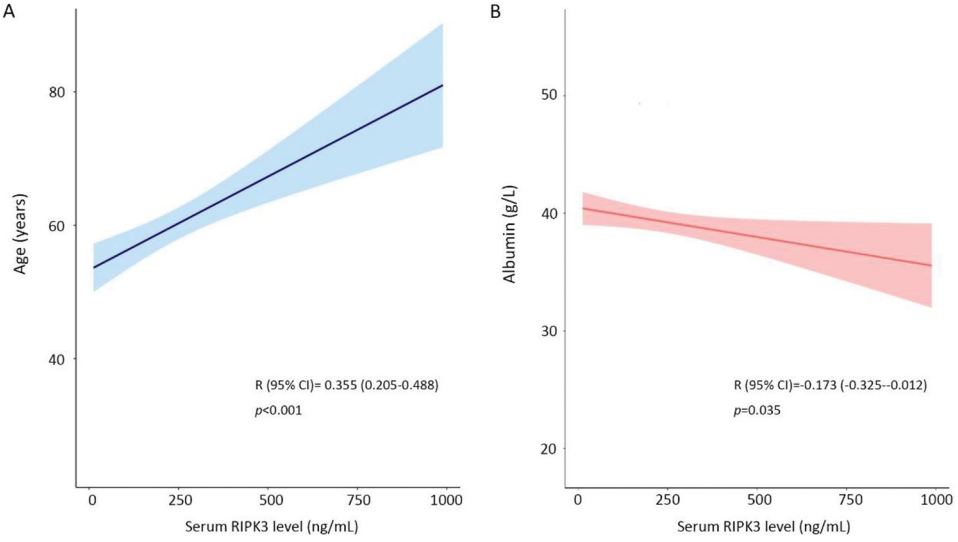

Fig. 4 Plasma RIPK3 concentration in relation to the age (**A**) and serum albumin levels (**B**)

mortality in patients receiving MHD. The optimal cutoff value was 251.54 ng/mL.

Furthermore, participants were stratified into groups on the basis of the plasma RIPK3 concentration to assess the risk of all-cause mortality. K–M estimates revealed a significantly greater overall survival probability for patients with RIPK3 concentrations lower than 251.5 ng/mL than for those with RIPK3 concentrations ≥ 251.5 ng/mL ($p < 0.001$; log-rank test) (Fig. 6).

Discussion

In this prospective observational study with a 4-year follow-up, the plasma level of RIPK3 independently predicted all-cause mortality in patients receiving MHD. To the best of our knowledge, this is the first study to show the independent relationship of circulating RIPK3 with all-cause death in a cohort of MHD patients.

Excessive inflammation is a key risk factor for both acute and chronic organ dysfunction [21–22]. As a serine/threonine kinase, RIPK3 is recognized as a critical mediator of necroptosis [23]. Because of the intracellular components released from rupturing necrotic cells, necroptosis induces subsequent inflammatory responses [12]. Notably, RIPK3 can trigger caspase-8-dependent apoptosis independent of its kinase function [24]. Additionally, RIPK3 can activate the NLRP3 inflammasome and the subsequent release of inflammatory cytokines in the absence of necroptotic activity [16]. Taken together, these findings illustrate the ability of RIPK3 to activate the inflammatory response via necroptosis-dependent and necroptosis-independent pathways. Given the crucial role of RIPK3 in inflammation, a series of studies were performed to explore the association between circulating RIPK3 levels and organ failure [25–26]. Ma et al. [13] reported that elevated levels of RIPK3 in the plasma of patients admitted to the ICU were associated with in-hospital mortality and organ failure. Ju and colleagues measured plasma RIPK3 levels in patients with coronary

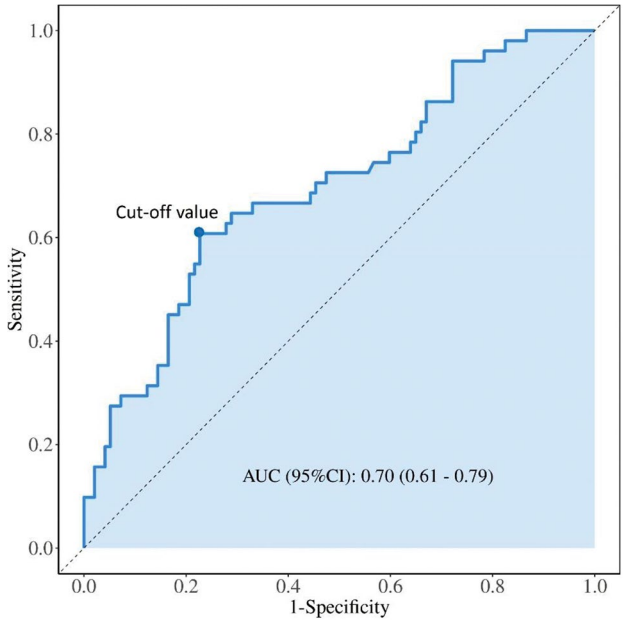

Fig. 5 ROC curve for the plasma RIPK3 level to predict all-cause death in MHD patients. AUC, area under the curve

artery disease (CAD) and demonstrated an independent association between plasma RIPK3 levels and CAD [18]. In addition, plasma RIPK3 concentrations were markedly higher in patients with acute ischemic stroke than in controls [25]. A two-center prospective cohort study revealed circulating RIPK3 to be a potential biomarker related to severity and prognosis after traumatic brain injury [20]. In the present study, we examined plasma RIPK3 levels in patients undergoing MHD treatment. The 4-year follow-up data revealed an independent relationship between plasma RIPK3 levels and all-cause death in patients with MHD.

Additionally, age and serum albumin levels were independently associated with all-cause mortality in our cohort. This result was consistent with previous investigations, which demonstrated that age and hypoalbuminemia conferred a higher mortality risk in patients receiving hemodialysis [27–28]. Recently, studies have further revealed the association between aging, hypoalbuminemia and inflammation [29–30]. Aging-related systemic chronic inflammation is clinically characterized by high serum concentrations of inflammatory cytokines as well as persistent infiltration of immune cells in virtually all systems [29]. As an indicator of nutritional status, serum albumin exhibited a close relationship with systemic inflammatory markers [30]. In the present study, our data showed a significant correlation between age, serum albumin and RIPK3. Thus, these findings provided more evidence to support the association of aging, malnutrition and inflammation correlated with high mortality in MHD patients.

Hemodialysis is a vital therapeutic strategy for patients with chronic renal failure. Numerous studies have revealed a high risk of death in patients undergoing hemodialysis, which is attributable to both cardiovascular (CV) and non-CV causes [4]. Further investigations revealed the predictive value of systemic inflammation markers, such as CRP and interleukin-6 (IL-6), for adverse outcomes and mortality in ESRD patients [26,

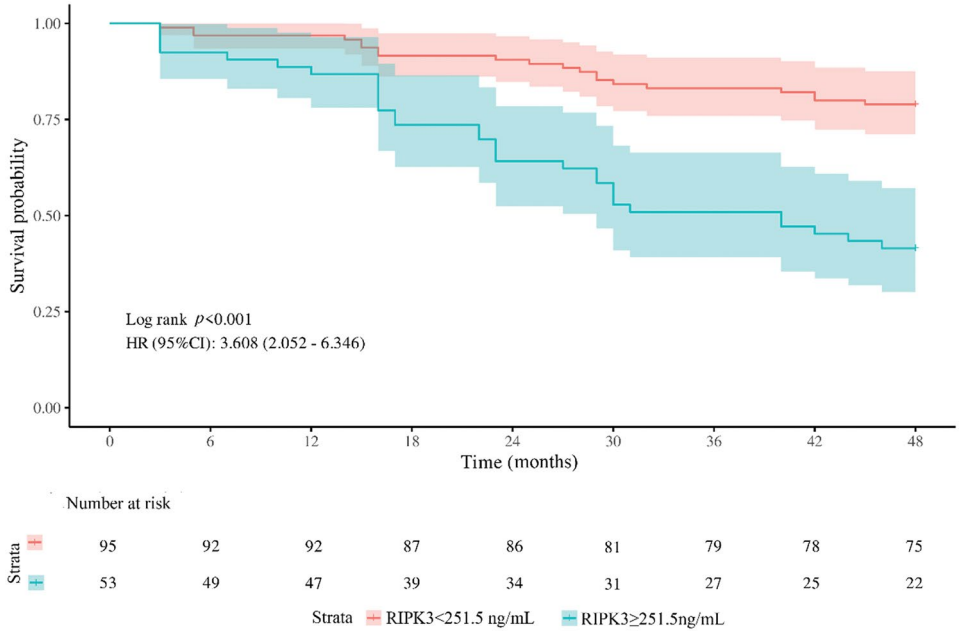

Fig. 6 The Kaplan-Meier estimate of overall survival in MHD patients with plasma RIPK3 level < 251.5ng/mL and ≥ 251.5ng/mL ($p < 0.001$; log-rank test)

31–32]. However, current measurements of these systemic inflammation markers reflect underlying nonspecific inflammatory processes. Recent studies have expanded the understanding of regulated cell death (including apoptosis, necroptosis, ferroptosis, and pyroptosis) as an important mechanism underlying inflammation [33–35]. Given the critical role of RIPK3 in the activation of necroptosis and apoptosis, the present study focused on the predictive value of RIPK3 for all-cause mortality in MHD patients via a 4-year follow-up. Our results revealed that patients with higher RIPK3 levels had an obviously greater incidence of all-cause death. Further univariate and multivariate Cox regression analyses revealed that circulating RIPK3 was a crucial independent predictor of all-cause mortality in the study population. These findings support the role of regulated cell death in organ dysfunction and suggest the potential application of RIPK3 as a biomarker for predicting death. Therefore, early monitoring and intervention of RIPK3 levels may be a target for improving MHD prognosis.

Certain limitations should be acknowledged. First, our study was a single-center study. Therefore, the sample size was relatively small, which limited our stratified analyses. Second, we could not adjust for all potential confounders that have been reported to be associated with mortality in MHD patients. Third, RIPK3 was measured only once at baseline, and we were unable to capture its dynamic changes over time. Consequently, it is imperative to conduct multicenter studies with larger sample sizes to monitor plasma RIPK3 dynamically in MHD patients in the future. Finally, the observational nature of the present study does not allow us to assess causality and the detailed mechanisms underlying the involvement of RIPK3 in mortality increase in MHD patients.

In conclusion, our study revealed that a higher plasma level of RIPK3 in patients receiving MHD treatment was associated with an increased risk of all-cause mortality. Thus, plasma RIPK3 may serve as a promising novel biomarker for risk stratification and guide the clinical management of MHD patients.

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Author contributions
Min Wu contributed to the study design and manuscript writing. Qian Sun, Kai-Di Zhang, Wei Sun and Min Gao contributed to data acquisition. Qing Wei and Meng-Ting Li contributed to data analysis. Liu-Ping Zhang contributed to the commentary and revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Data availability
The data involved in the present study are available from the corresponding author under reasonable request.

Declarations

Ethics approval and consent of participate
This study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Southeast University Zhongda Hospital (2019ZDSYLL110-P01). The informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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