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Association between neutrophil percentage-to-albumin ratio and mortality in Hemodialysis patients: insights from a prospective cohort study

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Abstract

Background The neutrophil percentage-to-albumin ratio (NPAR) emerges as a novel inflammation marker, demonstrating prognostic ability in a variety of cardiovascular diseases. However, its impact on mortality among patients undergoing maintenance hemodialysis (MHD) remains uncertain. Our research aims to determine whether NPAR is a reliable predictor of mortality in MHD patients.

Methods A total of 1803 MHD patients were recruited in this prospective cohort. Patients were stratified into three groups based on baseline NPAR levels. The association between NPAR and all-cause and cardiovascular mortality was evaluated using multivariate Cox proportional risk model and sensitivity analysis. NPAR's predictive performance was assessed using the receiver operating characteristic (ROC) curve, compared to several conventional biomarkers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), neutrophil count, and serum albumin. The area under the curve (AUC) values of NPAR and these biomarkers were compared using the DeLong's test.

Results Throughout a median follow-up period of 28 months, 239 (13.3%) patients died, with 91 (5.0%) dying of cardiovascular disease. Both all-cause mortality and cardiovascular mortality exhibited remarkably higher within the high NPAR group compared to the middle and low NPAR groups in the multivariate Cox regression analysis. The adjusted hazard ratio was 1.550 (95% CI: 1.110–2.166, $P=0.010$) for all-cause mortality and 1.844 (95% CI: 1.058–3.212, $P=0.031$) for cardiovascular mortality. This association was further corroborated by sensitivity analyses. The AUC values of NPAR for all-cause mortality and cardiovascular mortality were 0.612 (95% CI: 0.572–0.652, $P<0.001$) and 0.618 (95% CI: 0.557–0.678, $P<0.001$), separately. The p-values for comparing NPAR's AUC with those of NLR, PLR, neutrophils, and

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albumin were 0.307, 0.094, 0.014, and 0.154 for all-cause mortality, and 0.879, 0.126, 0.119, and 0.596 for cardiovascular mortality.

Conclusion High NPAR level was independently associated with a higher increased risk of death in MHD patients.

Keywords Maintenance Hemodialysis patients, Neutrophil percentage-to-albumin ratio, Mortality, Inflammation

Introduction

Chronic kidney disease (CKD) represents a significant and escalating public health challenge worldwide, affecting approximately 843.6 million people globally [1]. With declining renal function, hemodialysis is one of the dominant renal replacement therapy (RRT) options for end-stage kidney disease (ESKD) patients to improve their quality of life. Despite advancements in dialysis, mortality remains high among hemodialysis patients, especially in developed countries, contributing to a substantial health burden [2]. According to a recent report by the United States Renal Data System, arrhythmias and cardiac arrest were identified as the leading causes of death among hemodialysis patients, accounting for 47.1% of deaths with a known cause. Additionally, cardiovascular diseases, including stroke, were responsible for more than half (55.9%) of all known causes of death in this population [3].

A significant challenge for maintenance hemodialysis (MHD) patients is the malnutrition-inflammation-atherosclerosis (MIA) syndrome, which increases complications and mortality [4, 5]. Several factors contribute to MIA syndrome, such as comorbidities, uremic toxins, infections, and inadequate nutrient intake [6, 7]. These factors lead to persistent inflammation and malnutrition in MHD patients, which are linked to adverse clinical outcomes. Persistent inflammation also contributes to cardiovascular disease and malnutrition [8]. Therefore, the establishment of inflammation-related parameters for assessment of inflammatory status in MHD patients and identifying individuals who are at high risk of mortality is essential.

The neutrophil percentage-albumin ratio (NPAR), which represents a new combined marker comprising both neutrophil and serum albumin levels, has been proven a favorable predictive and prognostic value in various diseases, including cancer, stroke, spinal cord injury, acute kidney injury, and sepsis [9, 10, 11, 12, 13]. A recent study has reported its ability to predict mortality in peritoneal dialysis patients [14]. However, to our knowledge, the connection between NPAR and mortality in patients receiving maintenance hemodialysis remains unexplored. Hence, in this prospective cohort study, we evaluated the effect of NPAR on mortality among MHD patients and compared its prognostic value with other similar biomarkers, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), neutrophil count, and serum albumin.

Materials and methods

Study population

This multicenter, prospective, observational cohort study involved the collection of baseline clinical data from patients undergoing hemodialysis at 18 centers across Anhui Province, eastern China, from January to December 2020. Follow-up monitoring of these patients was conducted from January 2021 to May 2023. Participants meeting these criteria were included in the study: (1) age beyond 18 years; (2) Patients undergoing hemodialysis treatments for no less than three months. The following were established as exclusion criteria: (1) age over 80 years; (2) pregnancy, persistent infections, or combined severe brain, lung, liver, and other organ failure diseases, such as hemiplegia, chronic respiratory failure, cirrhosis, malignant tumors, psychosis, and other comorbidities; (3) Patients without follow-up information and unable to provide informed permission. Ethical approval for this study was granted by the Research Ethics Committee of the Second Affiliated Hospital of Anhui Medical University, following the principles of the Declaration of Helsinki (No. PJ-YX2020-006). Written informed consent was obtained from each subject.

Data collection

In this study, data were collected via Peking University's clinical data platform, "Six Yuan Space" [15]. Doctors who participated in the data collection received professional training. Each center registered on the platform for data acquisition, and the data were summarized and reviewed by the chief project manager for quality control. Clinical information was gathered on age, sex, body mass index, smoking status, duration of dialysis, and pre-dialysis blood pressure. Body mass index was calculated as patient weight/height^2 (kg/m^2). For smoking status, cessation of smoking for at least 3 months was considered to be a former smoker. Comorbidities were included hypertension, diabetes mellitus, cardiovascular and cerebrovascular diseases. Meeting any of the following criteria was recorded as hypertension: (1) Resting blood pressure measurements were taken on different days, with readings of ≥ 140/90 mmHg recorded on at least three occasions; (2) Patients previously diagnosed with hypertension who are currently receiving antihypertensive

drugs. Patients were deemed to have diabetes mellitus if they were clinically diagnosed with type I/II diabetes mellitus or currently receiving treatment with hypoglycemic drugs. The occurrence of any of the following conditions was defined as cardiovascular disease: myocardial infarction, congestive heart failure, coronary atherosclerotic heart disease, malignant arrhythmia, and cardiac arrest [16]. Cerebrovascular disease included cerebral infarction, transient ischemic attack, cerebral hemorrhage, and carotid endarterectomy [17]. Laboratory variables included white blood cells, neutrophils, lymphocytes, serum albumin, red blood cells, hemoglobin, hematocrit, platelets, alkaline phosphatase, creatinine, urea nitrogen, corrected calcium, serum phosphorus, and parathyroid hormone. A corrected serum calcium formula was applied when serum albumin was lower than 40 g/L. This formula was corrected Ca^{2+} (mmol/L) = total serum Ca^{2+} (mmol/L) + 0.2×[4-Alb (g/L)/10]. Treatment consisted of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, α/βreceptor blockers, calcium channel blockers, fibrates, and a history of parathyroidectomy.

Clinical outcomes

The principal endpoint investigated was all-cause mortality in this study, with cardiovascular mortality as a secondary endpoint. We ascertained the cause of death of patients through examination of medical charts, administering phone interviews with patients or their families, and directly communicating with referring physicians.

Statistical analysis

NPAR was measured as percentage of neutrophils divided by serum albumin. Participants' baseline NPAR levels were divided into three groups according to tertiles: low NPAR group (< 1.50, $n = 595$), middle NPAR group (1.50≤, < 1.76, $n = 612$) and high NPAR group (1.76≤, $n = 596$). Continuous variables with non-normal distributions were reported using the median and interquartile range (p25 and p75). Percentages were used for categorical variable descriptions. The Kruskal-Wallis test and chi-square test were utilized to examine the distinctions among NPAR groups. Given the inclusion of over 30 independent variables, we employed a two-step approach: first, univariate analyses, followed by multivariate analyses using Cox proportional hazards models. Only those variables that were statistically significant (p-values < 0.05) in the univariate analysis were included in the multivariate Cox roportional hazard model to explore the association between NPAR and both all-cause and cardiovascular mortality. Differences among the three groups were evaluated using the log-rank test, and survival analysis was conducted using Kaplan-Meier curves.

Receiver operating characteristic (ROC) curve analysis was utilized in estimating the prognostic capacity of NPAR and several traditional biomarkers, and calculated the area under the curve (AUC) for each biomarker. The DeLong's test was employed to assess differences in AUC between NPAR and other inflammatory markers. Subjects were classified into two groups according to the thresholds derived from the ROC curve analysis. Additionally, study participants were reclassified into two groups based on the median values of NPAR and NLR, respectively. The Kaplan-Meier curves were then re-evaluated to validate the robustness of our findings. SPSS 25.0 and R software (version, R-4.4.1) was conducted for statistical analysis. The p-value of less than 0.05 indicated statistical significance for all variables.

Results

Participant characteristics

The flowchart detailing the included participants was presented in Fig. 1. This study enrolled 1803 hemodialysis patients, with a median follow-up time of 28 months. The median age of the selected patients was 54 (45, 63) years, with 1071 (59.4%) male and 732 (40.6%) female. Additionally, the median BMI was 21.6 (19.3, 24.0) kg/m^2 and 1060 (58.8%) were never smokers. Among those patients, 1368 (75.9%) had hypertension, 434 (24.1%) had diabetes mellitus, 285 (15.8%) had a history of cardiovascular disease, and 140 (7.8%) had a history of cerebrovascular disease. Out of 239 (13.3%) all-cause deaths, 91 (5.0%) were due to cardiovascular diseases and another 148 (8.3%) were due to non-cardiovascular diseases. Table 1 showed comparisons of patients' characteristics by NPAR tertiles. Patients classified within the high NPAR group had higher age, BMI, leukocyte counts, neutrophil counts, and neutrophil percentage compared with those in the low and middle NPAR groups ($P < 0.05$). Lymphocyte count, serum albumin level, red blood cell count, hemoglobin, hematocrit, and creatinine were lower in the high NPAR group compared to the other groups ($P < 0.05$). All-cause mortality, cardiovascular mortality and non-cardiovascular mortality were also higher in the high NPAR group ($P < 0.05$).

Association between NPAR and all-cause and cardiovascular mortality

The results of the multifactorial Cox proportional hazards regression model were shown in Table 2. There were three models constructed in this study for examining the correlation between NPAR and all-cause as well as cardiovascular mortality. For NPAR and all-cause mortality: model 1 did not include any covariate adjustments; adjustments in model 2 included age, sex, and BMI; model 3, dialysis duration, systolic blood pressure, diabetes mellitus, history of cardiovascular disease,

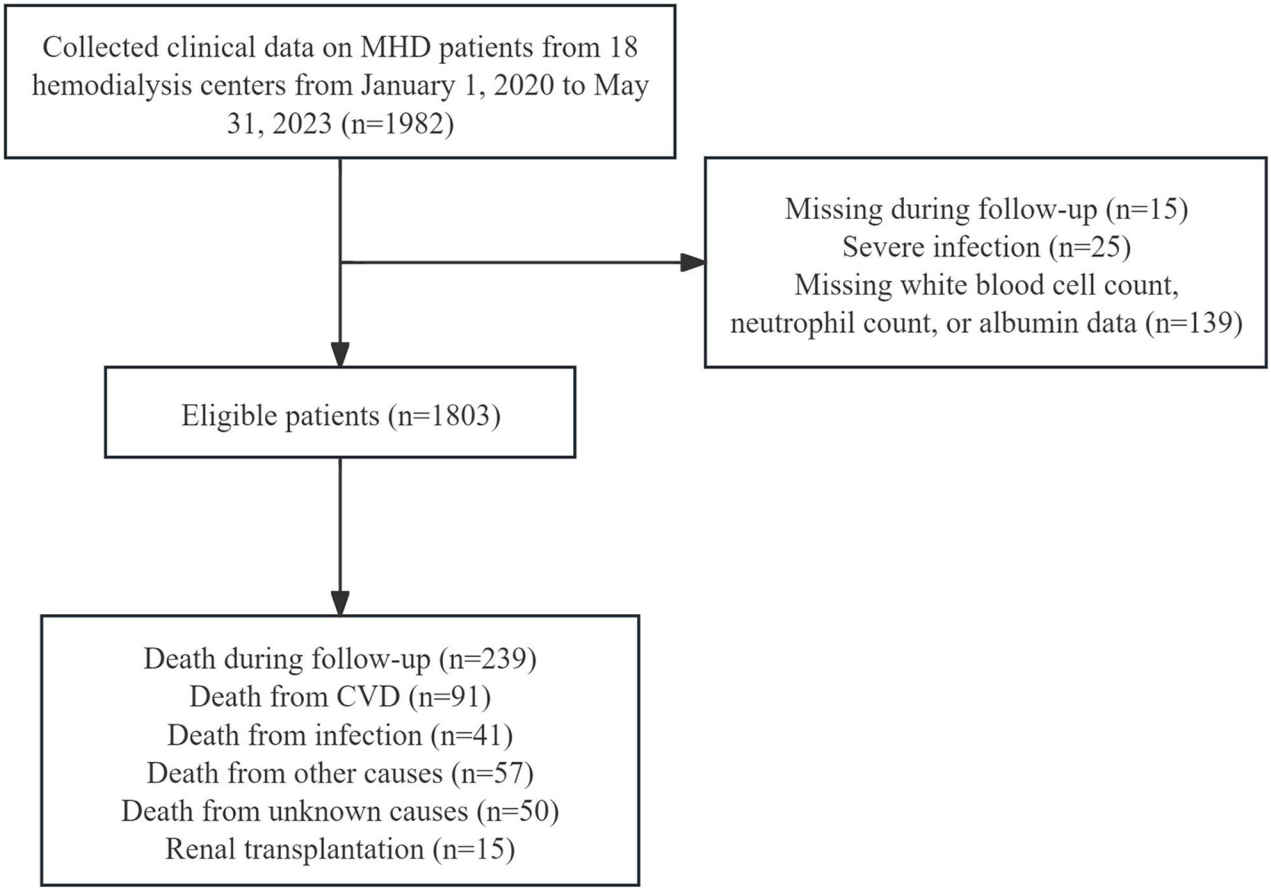

Fig. 1 Flow chart of the study population in this cohort. Abbreviations: MHD, maintenance hemodialysis; CVD, cardiovascular disease

parathyroidectomy, lymphocyte, serum creatinine, and phosphorus were added as covariates to the adjustments made in model 2. As for the NPAR and cardiovascular mortality modeled as follows: model 1, no adjustment for covariates; model 2 adjusted for age, sex, and BMI; model 3, model 2 plus dialysis duration, systolic blood pressure, diabetes mellitus, history of cardiovascular disease, history of cerebrovascular disease, lymphocyte, and serum creatinine. Hemodialysis patients with a high NPAR had a increased risk of all-cause mortality. This correlation was observed in model 1 (HR: 3.148 95% CI: 2.269–4.367, $P<0.001$); model 2 (Adjusted HR: 2.873, 95% CI: 2.03–4.065, $P<0.001$) and model 3 (Adjusted HR: 1.924, 95% CI: 1.329–2.784, $P=0.001$) were significant. Similarly, a high NPAR was remarkably related to an increased likelihood of cardiovascular death. This relationship was also apparent in model 1 (HR: 3.609, 95% CI: 2.177–5.984, $P<0.001$); model 2 (Adjusted HR: 3.300, 95% CI: 1.916–5.685, $P<0.001$) and model 3 (Adjusted HR: 2.352, 95% CI: 1.308–4.230, $P=0.004$). Moreover, we obtained consistent results by converting NPAR from a continuous variable to a tertiary variable (Table 2). Kaplan-Meier curves depicting cardiovascular and all-cause mortality across different NPAR levels were presented in Fig. 2. Compared to patients in the middle and low NPAR groups, Patients undergoing hemodialysis within the high NPAR group encountered a greater cardiovascular mortality (*log-rank* = 19.148, $P<0.001$) and all-cause mortality (*log-rank* = 39.895, $P<0.001$). The findings of the univariate Cox regression analysis were given in Supplementary Table 1.

Comparison of prognostic value of NPAR with several biomarkers

The ROC curve and area under the curve (AUC) were exhibited in Fig. 3; Table 3, separately. For all-cause mortality, the AUC value for NPAR was 0.612 (95%CI: 0.572–0.652, $P<0.001$), NLR was 0.630 (95%CI: 0.592–0.668, $P<0.001$), PLR was 0.573 (95%CI: 0.534–0.612, $P<0.001$), neutrophil count was 0.558 (95%CI: 0.519–0.597, $P=0.004$) and serum albumin was 0.589 (95%CI: 0.550–0.627, $P<0.001$). The AUC values related to cardiovascular mortality were 0.618 (95% CI: 0.572–0.652, $P<0.001$) for NPAR, 0.614 (95% CI: 0.558–0.671, $P<0.001$) in relation to NLR, 0.564 (95% CI: 0.505–0.624, $P=0.038$) pertaining to PLR, 0.572 (95% CI: 0.514–0.630, $P=0.021$) for

Table 1 Baseline characteristics of the study patients stratified by neutrophil percentage-to-albumin ratios

	Total	Low NPAR group	Middle NPAR group	High NPAR group	*P* value
	(*n* = 1803)	(< 1.50, *n* = 595)	(1.50≤, < 1.76, *n* = 612)	(1.76≤, *n* = 596)	
Demographic data					
Age(years)	54(45,63)	52(44,59)	54(45,63)	55(47,65)	< 0.001
Male sex(%)	1071(59.4)	371(62.4)	359(58.7)	341(57.2)	0.176
BMI(Kg/m^2)	21.6(19.3,24.0)	21.1(19.1,23.9)	21.7(19.6,23.9)	21.8(19.4,24.4)	0.040
Follow-up time(months)	28(23,32)	30(24,32)	30(24,32)	28(19,31)	< 0.001
Dialysis time(months)	75(50,111)	78(51,108)	76(52,115)	74(43,110)	0.095
Systolic BP(mmHg)	140(128,156)	140(128,154)	141(129,157)	141(126,157)	0.490
Diastolic BP(mmHg)	80(71,90)	81(72,90)	80(71,90)	80(70,90)	0.104
Smoking status(%)					0.178
Never	1060(58.8)	342(57.5)	347(56.7)	371(62.2)	
Current	280(15.5)	87(14.6)	105(17.2)	88(14.8)	
Former	463(25.7)	166(27.9)	160(26.1)	137(23.0)	
Comorbidity					
Hypertension (%)	1368(75.9)	472(79.3)	464(75.8)	432(72.5)	0.022
Diabetes mellitus(%)	434(24.1)	101(17.0)	142(23.2)	191(32.0)	< 0.001
Cardiovascular disease(%)	285(15.8)	83(13.9)	87(14.2)	115(19.3)	0.017
Cerebrovascular disease(%)	140(7.8)	39(6.6)	42(6.9)	59(9.9)	0.058
Laboratory variables					
NPAR	1.62(1.43,1.84)	1.35(1.23,1.43)	1.62(1.56,1.69)	1.94(1.84,2.11)	< 0.001
WBC(*10^9/L)	6.1(5.0,7.3)	6.0(5.0,7.1)	6.0(4.9,7.3)	6.1(5.0,7.7)	0.025
Neutrophil count(*10^9/L)	3.9(3.2,4.9)	3.4(2.8,4.2)	4.0(3.3,4.9)	4.4(3.5,5.6)	< 0.001
Neutrophil percentage	0.67(0.61,0.72)	0.59(0.53,0.64)	0.67(0.63,0.71)	0.73(0.69,0.77)	< 0.001
Lymphocyte(*10^9/L)	1.3(1,1.6)	1.4(1.1,1.8)	1.2(1.0,1.6)	1.1(0.8,1.4)	< 0.001
Albumin(g/L)	41(37.4,44.4)	44.6(41.4,47.1)	41.5(39.0,44.0)	36.9(34.2,39.4)	< 0.001
RBC(*10^9/L)	3.6(3.2,4)	3.7(3.3,4.2)	3.6(3.2,4.0)	3.5(3.1,3.9)	< 0.001
Hemoglobin(g/L)	110(99,121)	113(102,125)	110(99,121)	106(94,117)	< 0.001
Hct	34.1(30.7,38.0)	35.4(31.5,39.0)	34.2(31.0,38.0)	33.0(29.0,36.8)	< 0.001
Platelet(*10^9/L)	157(121,199)	158(126,197)	157(119,199)	155(117,203)	0.513
ALP(U/L)	87(67,116)	88(68,117)	87(65,119)	86(69,112)	0.771
Cr(μmol/L)	845(677,1024)	854(689,1046)	868(681,1046)	821(660,988)	0.009
BUN(mmol/L)	21(16.2,26.2)	20.2(15.7,24.9)	21.5(16.9,26.4)	21.4(16.3,27.1)	< 0.001
Corrected Ca^{2+}(mmol/L)	2.31(2.17,2.45)	2.33(2.18,2.44)	2.30(2.18,2.46)	2.29(2.15,2.45)	0.228
Phosphorus(mmol/L)	1.8(1.5,2.2)	1.8(1.5,2.2)	1.9(1.5,2.2)	1.8(1.4,2.2)	0.032
iPTH(pg/ml)	314.5(156.0,581.0)	331.0(151.7,605.4)	317.1(169.3,580.4)	287.3(147.4,534.7)	0.274
Treatments					
ACEI(%)	105(5.8)	34(5.7)	36(5.9)	35(5.9)	0.990
ARB(%)	356(19.7)	115(19.3)	129(21.1)	112(18.8)	0.579
Short CCB(%)	82(4.5)	32(5.4)	24(3.9)	26(4.4)	0.462
Long CCB(%)	941(52.2)	308(51.8)	331(54.1)	302(50.7)	0.478
α-receptor blocker(%)	76(4.2)	29(4.9)	25(4.1)	22(3.7)	0.586
β-receptor blocker(%)	356(19.7)	122(20.5)	126(20.6)	108(18.1)	0.476
α + β receptor blocker(%)	39(2.2)	9(1.5)	14(2.3)	16(2.7)	0.368
Fibrates(%)	204(11.3)	63(10.6)	75(12.3)	66(11.1)	0.642
Parathyroidectomy (%)	117(6.5)	43(7.2)	39(6.4)	35(5.9)	0.631
Cause of death					
All-cause mortality(%)	239(13.3)	58(9.7)	63(10.3)	118(19.8)	< 0.001
Cardiovascular mortality(%)	91(5.0)	20(3.4)	24(3.9)	47(7.9)	0.001
Non-cardiovascular mortality(%)	148(8.3)	38(6.3)	39(6.4)	71(11.9)	0.001

Abbreviations: NPAR, neutrophil percentage-to-albumin ratio; BMI, body mass index; BP, blood pressure; WBC, white blood cell; RBC, red blood cell; Hct, hematocrit; ALP, alkaline phosphatase; Cr, creatinine; BUN, blood urea nitrogen; iPTH, immunoreactive parathyroid hormone; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blockers

Table 2 Association of the neutrophil percentage-to-albumin ratios with all-cause mortality and cardiovascular mortality

	Model 1		Model 2		Model 3	
	HR (95%CI)	***P* value**	**HR (95%CI)**	***P* value**	**HR (95%CI)**	***P* value**
All-cause mortality						
NPAR(Continuous)	3.148(2.269–4.367)	< 0.001	2.873(2.03–4.065)	< 0.001	1.924(1.329–2.784)	0.001
NPAR(Categories)						
Low NPAR group	Reference	Reference	Reference	Reference	Reference	Reference
Middle NPAR group	1.052(0.736–1.503)	0.782	0.987(0.690–1.412)	0.945	0.891(0.620–1.280)	0.533
High NPAR group	2.273(1.659–3.114)	< 0.001	1.992(1.449–2.738)	< 0.001	1.550(1.110–2.166)	0.010
Cardiovascular mortality						
NPAR(Continuous)	3.609(2.177–5.984)	< 0.001	3.300(1.916–5.685)	< 0.001	2.352(1.308–4.230)	0.004
NPAR(Categories)						
Low NPAR group	Reference	Reference	Reference	Reference	Reference	Reference
Middle NPAR group	1.166(0.644–2.111)	0.612	1.089(0.600-1.973)	0.780	1.011(0.554–1.845)	0.972
High NPAR group	2.627(1.556–4.434)	< 0.001	2.273(1.340–3.854)	0.002	1.844(1.058–3.212)	0.031

Model 1: unadjusted; Model 2: adjusted for age, sex, BMI; Model 3 for all-cause mortality: adjusted for model 2 and dialysis duration, systolic blood pressure, diabetes mellitus, history of cardiovascular disease, parathyroidectomy, lymphocyte, serum creatinine, and phosphorus. Model 3 for cardiovascular mortality: adjusted for model 2 and dialysis duration, systolic blood pressure, diabetes mellitus, history of cardiovascular disease, history of cerebrovascular disease, lymphocyte, and serum creatinine

Abbreviations: HR, hazard ratio; CI, confidence interval

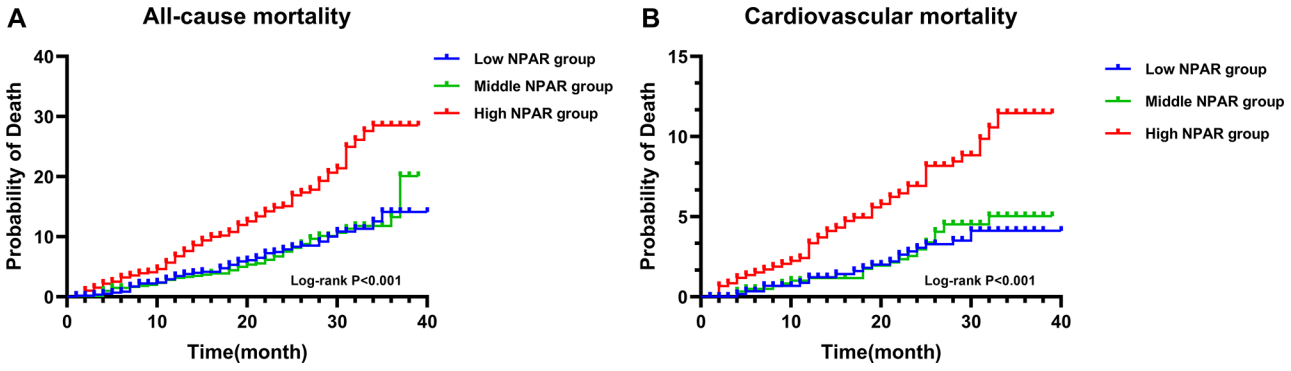

Fig. 2 Kaplan-Meier curves for mortality according to NPAR tertiles

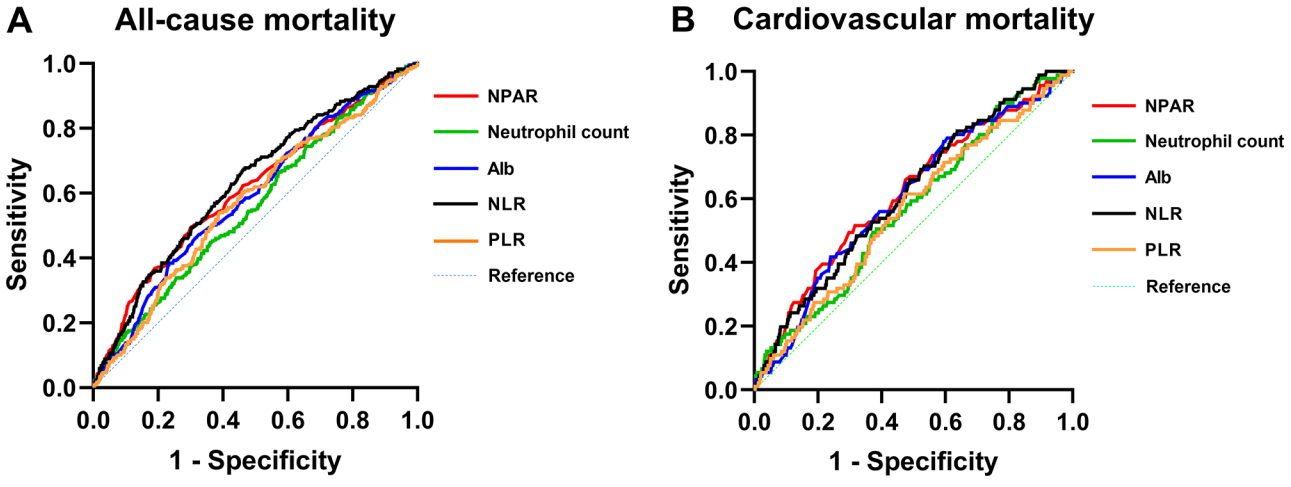

Fig. 3 The ROC curves of NPAR, Neutrophil count, Alb, NLR and PLR for predicting mortality

Table 3 Area under ROC curve for several biomarkers

	All-cause mortality			Cardiovascular mortality		
	AUC	**95%CI**	***P* value**	**AUC**	**95%CI**	***P* value**
NPAR	0.612	0.572–0.652	< 0.001	0.618	0.557–0.678	< 0.001
Neutrophil count	0.558	0.519–0.597	0.004	0.572	0.514–0.630	0.021
Alb	0.589	0.550–0.627	< 0.001	0.604	0.546–0.663	0.001
NLR	0.630	0.592–0.668	< 0.001	0.614	0.558–0.671	< 0.001
PLR	0.573	0.534–0.612	< 0.001	0.564	0.505–0.624	0.038

Abbreviations: AUC, area under the ROC curve; NPAR, neutrophil percentage-to-albumin ratio; Alb, albumin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio

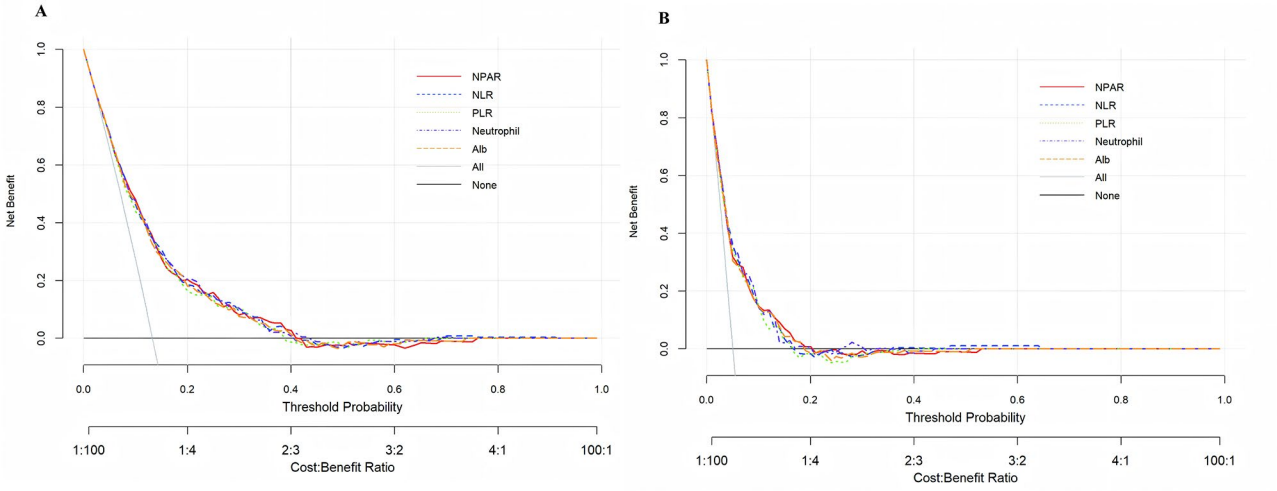

Fig. 4 DCA curves for NPAR and other markers in predicting all-cause (**A**) and cardiovascular mortality (**B**)

neutrophil count, and serum albumin was 0.604 (95% CI: 0.546–0.663, $P = 0.001$). In the present study, NPAR demonstrated a higher AUC value for predicting cardiovascular mortality compared to NLR, PLR, neutrophil count, and serum albumin. However, the DeLong's test revealed no statistically significant difference in AUC between NPAR and these inflammatory markers ($P > 0.05$). Similarly, while the AUC value of NPAR was slightly lower than that of NLR for predicting all-cause mortality, the DeLong's test again indicated no significant difference in AUC between the two ($P > 0.05$). Notably, the DeLong's test comparing the AUC between NPAR and neutrophil counts suggested that NPAR was a stronger predictor of all-cause mortality than neutrophil counts alone. The DeLong's test results of NPAR with other markers were summarized in Supplementary Table 2.

Decision curve analysis

Clinical decision curves for the prediction of all-cause and cardiovascular mortality using NPAR and other markers such as NLR, PLR, neutrophil count, and albumin were shown in Fig. 4. For all-cause mortality, the net benefit of the NPAR, NLR, PLR, neutrophil, and albumin curves was higher than that of the "all-patient intervention" and "no intervention" strategies within the thresholds of 0.01–0.408, 0.01–0.405 and 0.696–0.928, 0.01–0.386, 0.01–0.433, and 0.01–0.407, respectively. These findings suggested that, within these specific threshold intervals, these markers were effective in differentiating patients at high risk of death. For the prediction of cardiovascular mortality, the thresholds for the NPAR curve ranged from 0.01 to 0.206, the NLR curve from 0.01 to 0.167 and 0.356 to 0.652, the PLR curve from 0.01 to 0.164, the neutrophil curve from 0.01 to 0.202, 0.260 to 0.308, and 0.336–0.352, and the albumin curve from 0.01 to 0.185. Within these ranges, the net benefits of the curves were significantly higher than those of the "all-patient intervention" and "no intervention" strategies. These results indicated that each of the markers evaluated provided a higher net benefit compared to the extremes of "All" and "None". The decision curve analysis (DCA) curves for NPAR and other markers, plotted separately for all-cause and cardiovascular mortality prediction, were shown in Supplementary Fig. 1-5 and Fig. 6-10.

Sensitivity analysis

The ROC curve analysis determined that the optimal threshold of NPAR for predicting all-cause mortality was 1.765, with a sensitivity of 0.494 and a specificity of 0.699. Based on this threshold, patients were categorized into

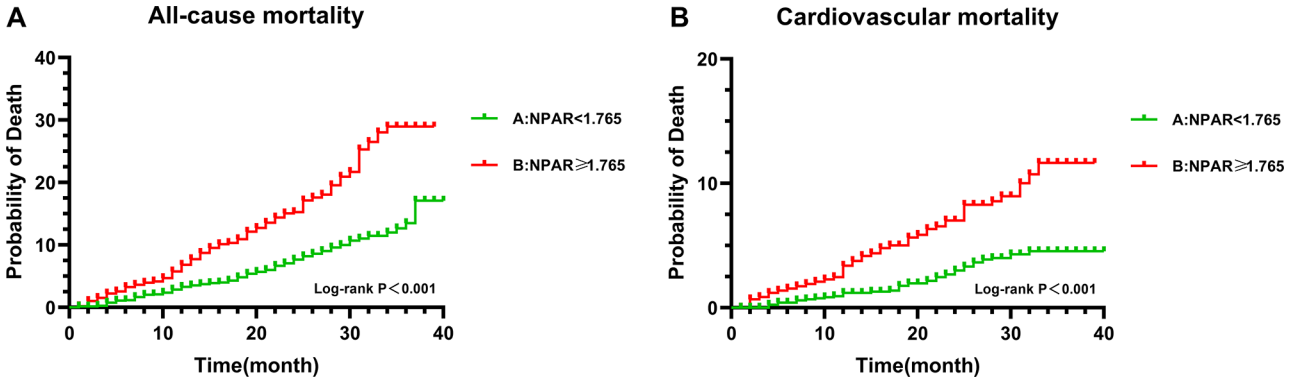

Fig. 5 Kaplan-Meier curves for mortality in two patient groups classified by ROC-derived thresholds

two groups: group A (NPAR < 1.765), which consisted of 588 patients, and group B (NPAR ≥ 1.765), which comprised 1215 hemodialysis patients. Similarly, for predicting cardiovascular mortality, the ROC-derived threshold for NPAR was also 1.765, corresponding to a sensitivity of 0.516 and a specificity of 0.684. Patients were divided into the same groups (group A and group B) according to this threshold. As illustrated in Fig. 5, the Kaplan-Meier curves for both all-cause mortality and cardiovascular mortality showed significant differences between the two groups ($P < 0.001$). Specifically, patients in group B (NPAR ≥ 1.765) had significantly higher rates of all-cause mortality (log-rank = 42.299, $P < 0.001$) and cardiovascular mortality (log-rank = 19.946, $P < 0.001$) compared to patients in group A (NPAR < 1.765). Similar results were observed for the two groups stratified by the median values of NPAR and NLR. Their Kaplan-Meier curves are depicted in Supplementary Fig. 13-14.

Discussion

Our findings manifested a significant correlation between higher NPAR and heightened risks of both all-cause and cardiovascular mortality among MHD patients. After adjusting for confounders, the high NPAR group remained remarkably connected to all-cause and cardiovascular mortality compared with patients in the moderate NPAR and low NPAR groups. Additionally, sensitivity analyses further demonstrated that MHD patients with higher NPAR levels experienced higher all-cause and cardiovascular mortality. Similar to the other four biomarkers, NPAR also showed some potential in predicting both all-cause and cardiovascular mortality. Notably, this was the first research to evaluate the predictive potential of NPAR in hemodialysis patients, which implied that NPAR might be a promising parameter for predicting adverse prognosis.

Two critical risk factors that contribute to mortality in patients with chronic kidney disease are inflammation and malnutrition [18]. The causes of chronic inflammation associated with MHD patients include hypoxia, oxidative stress, immune dysfunction, and uremic toxins [8]. Persistent chronic inflammation is recognized to confer many complications including atherosclerosis, which enhances the risk of worse prognosis in MHD patients [19, 20]. Neutrophils play an essential role in both acute and chronic inflammation, contributing to innate immunity and infection, and their levels reflect the intensity of inflammation and infection in the body [21, 22]. Several investigations have confirmed that elevated neutrophils are related to a higher mortality rate in patients with end-stage renal disease [23, 24, 25]. Serum albumin, an important protein involved in antioxidant and anti-inflammatory functions, is frequently cited as a key clinical indicator of nutritional status [26]. Factors such as persistent chronic inflammation, lower nutrient intake, decreased synthesis, altered catabolism, and renal dialysis can lead to diminished serum albumin levels. Serum albumin levels are often reduced in MHD patients, reflecting malnutrition and systemic inflammation [27]. Low albumin levels have also been shown to be a valid predictor of mortality risk in MHD patients [28]. Chronic inflammation, which is frequently observed in MHD patients, can exacerbate malnutrition by reducing protein intake, increasing muscle catabolism, and suppressing appetite [29]. The interaction between inflammation and malnutrition affects both the metabolism and synthesis of albumin, leading to lower serum albumin concentrations [30].

NPAR refers to the ratio of neutrophil percentage to albumin level, with a high NPAR typically resulting from either an elevated neutrophil count or a decreased albumin level. Unlike single biomarkers, NPAR encompasses both the inflammatory and nutritional status of the patient, making it more indicative of unfavorable clinical outcomes. Extensive literature supported the predictive value of NPAR, illustrating its superiority over both neutrophil percentage and serum albumin as a prognostic marker. In various non-renal diseases, for example, a study that included 2,166 critically ill patients with severe sepsis or septic shock found that higher NPAR

was correlated with an elevated risk of all-cause mortality at 30, 90, and 365 days in these patients [14]. Even after adjusting for confounding variables, another study involving stroke patients indicated a notable correlation between elevated NPAR levels and a heightened probability of all-cause mortality [12]. High levels of NPAR have also been proved to independently contribute to the increased risk of all-cause mortality in patients with various cardiovascular diseases, such as atrial fibrillation, coronary artery disease, heart failure, and cardiogenic shock [31, 32, 33]. Recent findings from a longitudinal study found that higher NPAR is independently correlated with a greater risk of death in community-dwelling U.S. adults with COPD [34]. On the other hand, the role of NPAR has been evidenced in patients with renal disease. A study involving 1966 patients receiving peritoneal dialysis in a retrospective cohort design found a heightened risk of all-cause and cardiovascular mortality linked to elevated NPAR levels [35]. High levels of NPAR have equally been confirmed as an independent predictor of all-cause mortality in critically ill patients with acute kidney injury [15].

Despite these evidences, the link between NPAR and mortality for patients undergoing MHD is uncertain. Our results revealed that the risk of all-cause and cardiovascular mortality in the highest tertile of NPAR was 1.550 and 1.844 times higher than that in the lowest tertile, respectively. This suggested a worse prognosis for MHD patients with elevated NPAR levels. Besides, it has been previously shown that several classical biomarkers such as NLR and PLR have been shown to predict mortality in MHD patients [36, 37, 38]. The predictive ability of the biomarkers examined in this study was demonstrated through various analyses. We compared the AUC values of NPAR with those of other biomarkers and assessed the differences between them. The results revealed that, while the AUC of NPAR for predicting all-cause mortality exceeded that of PLR, neutrophils, and serum albumin, it was lower than that of NLR. According to the DeLong's test, no significant difference was found between the AUC values of NPAR and those of NLR, PLR, neutrophils, and serum albumin ($P > 0.05$). The only significant difference was observed when comparing the AUC of NPAR with neutrophils ($P < 0.05$). This finding indicates that NPAR, as a composite biomarker, has superior predictive performance for all-cause mortality in MHD patients compared to a single neutrophil count. In predicting cardiovascular mortality, although the AUC of NPAR was higher than that of other markers, the DeLong's test showed no significant difference in AUC values between NPAR and the other biomarkers ($P > 0.05$). Furthermore, the decision curve analysis (DCA) for NPAR and the other biomarkers revealed that these biomarkers were effective in distinguishing high-risk patients within specific threshold ranges, thus offering valuable insights for clinical decision-making. It is worth noting that the DCA analysis also revealed that the threshold range for NPAR in predicting all-cause mortality is between 0.01 and 0.408, whereas the threshold range for NLR spans from 0.01 to 0.405 and 0.696 to 0.928. While both markers have similar lower threshold ranges, the NLR's threshold extends further into higher values, suggesting a broader range of risk assessment. This suggests that NLR performs well across a broader threshold range, demonstrating more stable clinical predictive ability. In contrast, NPAR exhibited a narrower range of net benefit, predominantly focused on the low-risk category, indicating that it may be more suitable for the early screening or management of low-risk patients. In addition to predicting all-cause mortality, the threshold ranges for NLR and NPAR in predicting cardiovascular mortality also showed similar patterns. Specifically, the NLR threshold ranges from 0.01 to 0.167 and 0.356 to 0.652, while the NPAR threshold range spans from 0.01 to 0.206. This indicates that NLR has a broader range of predictive thresholds, allowing it to identify a wider group of high-risk patients. Additionally, NLR requires only the neutrophil-to-lymphocyte ratio, which is simple to calculate and easy to implement in clinical practice. However, NPAR necessitates the measurement of serum albumin, adding complexity and potential cost, especially in resource-limited settings. Overall, although the predictive power of NPAR did not surpass that of NLR in this study, it highlights the potential of this biomarker, which integrates inflammatory (neutrophils) and nutritional (albumin) parameters. This dual focus may provide a more comprehensive understanding of the pathophysiologic status of MHD patients. NPAR's emphasis on both inflammation and nutrition could offer some valuable insights for assessing inflammatory and nutritional status, particularly in specific patient subgroups such as those with severe malnutrition or chronic inflammation. Therefore, further studies are warranted to validate the incremental utility of NPAR and to explore its potential role as an adjunct biomarker.

This study has several strengths. For instance, its relatively large sample size contributes to improved representativeness. Additionally, as a multicenter, prospective cohort study, it provides a solid foundation for reliability. Nonetheless, it's essential to acknowledge certain limitations. Firstly, this study carries the possibility of follow-up bias, which could affect the accuracy of the results. Secondly, both neutrophil percentage and albumin were continuously and dynamically changing, we collected variables only at baseline, which may introduce random errors. Thirdly, even though we exerted our best efforts to control for bias using multivariate modes, there were still other known or unknown factors. Fourthly, due to a

lack of data, we were unable to collect additional inflammatory markers such as C-reactive protein, interleukin-6, and procalcitonin for comparison with NPAR. Furthermore, key parameters related to hemodialysis, including dialysis adequacy (expressed as Kt/V urea), type of vascular access, dialysis filter use, and dialysate glucose composition, were also not collected and thus not included in this study. Finally, considering the potential racial disparities in susceptibility to hypoalbuminemia, further validation of our findings is warranted across diverse racial populations.

Conclusion

In conclusion, our research established that in patients with MHD, a high level of NPAR was independently linked to both all-cause and cardiovascular mortality. NPAR could potentially serve as a valuable biomarker for predicting unfavorable prognosis of MHD patients.

Abbreviations

CKD	Chronic kidney disease
MHD	Maintenance hemodialysis
ROC	Receiver operating characteristic curve
NPAR	Neutrophil percentage-to-albumin ratio
NLR	Neutrophil-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio
RRT	Renal replacement therapy
ESKD	End-stage kidney disease
MIA	Malnutrition-inflammation-atherosclerosis syndrome

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-025-04027-0 .

Supplementary Material 1: Supplementary Figure 1: DCA curve for NPAR in predicting all-cause mortality(A).

Supplementary Material 2: Supplementary Figure 2: DCA curve for NLR in predicting all-cause mortality(B).

Supplementary Material 3: Supplementary Figure 3: DCA curve for PLR in predicting all-cause mortality(C).

Supplementary Material 4: Supplementary Figure 4: DCA curve for neutrophil in predicting all-cause mortality(D).

Supplementary Material 5: Supplementary Figure 5: DCA curve for albumin in predicting all-cause mortality(E).

Supplementary Material 6: Supplementary Figure 6: DCA curve of NPAR in predicting cardiovascular mortality(A).

Supplementary Material 7: Supplementary Figure 7: DCA curve of NLR in predicting cardiovascular mortality(B).

Supplementary Material 8: Supplementary Figure 8: DCA curve of PLR in predicting cardiovascular mortality(C).

Supplementary Material 9: Supplementary Figure 9: DCA curve of neutrophil in predicting cardiovascular mortality(D).

Supplementary Material 10: Supplementary Figure 10: DCA curve of albumin in predicting cardiovascular mortality(E).

Supplementary Material 11: Supplementary Figure 11: Kaplan-Meier curves for all-cause mortality(A) based on median NPAR value.

Supplementary Material 12: Supplementary Figure 12: Kaplan-Meier curves for cardiovascular mortality(B) based on median NPAR value.

Supplementary Material 13: Supplementary Figure 13: Kaplan-Meier curves for all-cause mortality(A) grouped by median NLR levels.

Supplementary Material 14: Supplementary Figure 14: Kaplan-Meier curves for cardiovascular mortality(B) grouped by median NLR levels.

Supplementary Material 15: Supplementary Table 2: DeLong's test for NPAR and other inflammatory markers.

Supplementary Material 16: Supplementary Table 1: Univariate Cox regression for all-cause and cardiovascular mortality.

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Author contributions

Jiaxin Zhu and Rui Shi contributed substantially to the paper's conception, data acquisition, analysis, and drafting. Xunliang Li and Mengqian Liu critically reviewed significant intellectual content and contributed to data acquisition, analysis, or interpretation. Linfei Yu, Youwei Bai, Yong Zhang, Wei Wang, Lei Chen, Guangcai Shi, Zhi Liu, Yuwen Guo, Jihui Fan, Shanfei Yang, Xiping Jin, Fan Zhang, Xiaoying Zong, Xiaofei Tang, Jiande Chen, Tao Ma and Bei Xiao provided access to the data and participated in patient registration and data collection. Deguang Wang designed the study and approved the final version for publication.

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Data availability

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

Declarations

Ethics approval and consent to participate

Approval for this survey was granted by the Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (No. PJ-YX2020-006). Informed consent was obtained from all participants before their enrollment in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

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References

1. Jager KJ, Kovesdy C, Langham R, et al. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. Nephrol Dial Transpl. 2019;34:1803–5.
2. Cockwell P, Fisher LA. The global burden of chronic kidney disease. Lancet. 2020;395:662–4.
3. United States Renal Data System. 2024 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2024.
4. Stenvinkel P. Inflammatory and atherosclerotic interactions in the depleted uremic patient. Blood Purif. 2001;19:53–61.
5. Allawi AAD. Malnutrition, inflamation and atherosclerosis (MIA syndrome) in patients with end stage renal disease on maintenance Hemodialysis (a single centre experience). Diabetes Metab Syndr. 2018;12:91–7.
6. Hung SC, Lai YS, Kuo KL et al. Volume overload and adverse outcomes in chronic kidney disease: clinical observational and animal studies. J Am Heart Assoc. 2015;4.
7. Kalantar-Zadeh K, Ikizler TA, Block G, et al. Malnutrition-inflammation complex syndrome in dialysis patients causes and consequences. Am J Kidney Dis. 2003;42:864–81.
8. Cobo G, Lindholm B, Stenvinkel P. Chronic inflammation in end-stage renal disease and dialysis. Nephrol Dial Transpl. 2018;33:iii35–40.
9. Chen Z, Xie D, Li Y, et al. Neutrophil albumin ratio is associated with All-Cause mortality in stroke patients: A retrospective database study. Int J Gen Med. 2022;15:1–9.
10. Ferro M, Babă DF, de Cobelli O, et al. Neutrophil percentage-to-albumin ratio predicts mortality in bladder cancer patients treated with neoadjuvant chemotherapy followed by radical cystectomy. Future Sci OA. 2021;7:FSO709.
11. Gong Y, Li D, Cheng B, et al. Increased neutrophil percentage-to-albumin ratio is associated with all-cause mortality in patients with severe sepsis or septic shock. Epidemiol Infect. 2020;148:e87.
12. Wang B, Li D, Cheng B et al. The neutrophil Percentage-to-Albumin ratio is associated with All-Cause mortality in critically ill patients with acute kidney injury. Biomed Res Int. 2020:5687672.
13. Wang C, Yu X, Wang T, et al. Association between neutrophil percentage-to-albumin ratio and pneumonia in patients with traumatic spinal cord injury. Spinal Cord. 2023;61:106–10.
14. Gao Y, Han Z, Feng X et al. Association of neutrophil and albumin with mortality risk in patients receiving peritoneal Dialysis. J Ren Nutr. 2023.
15. Tao S, Li X, Liu Z, et al. Investigation on maintenance Hemodialysis patients with mineral and bone disorder in Anhui Province, China. Int Urol Nephrol. 2023;55:389–98.
16. Cozzolino M, Mangano M, Stucchi A, et al. Cardiovascular disease in dialysis patients. Nephrol Dial Transpl. 2018;33:iii28–34.
17. Delmez JA, Yan G, Bailey J, et al. Cerebrovascular disease in maintenance Hemodialysis patients: results of the HEMO study. Am J Kidney Dis. 2006;47:131–8.
18. Peev V, Nayer A. Dyslipidemia, malnutrition, inflammation, cardiovascular disease and mortality in chronic kidney disease. Curr Opin Lipidol. 2014;25:54–60.
19. Stenvinkel P, Heimbürger O, Paultre F, et al. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. Kidney Int. 1999;55:1899–911.
20. Zimmermann J, Herrlinger S, Pruy A, et al. Inflammation enhances cardiovascular risk and mortality in Hemodialysis patients. Kidney Int. 1999;55:648–58.
21. Taleb S. Inflammation in atherosclerosis. Arch Cardiovasc Dis. 2016;109:708–15.
22. Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. Nat Rev Immunol. 2013;13:159–75.
23. Lano G, Sallee M, Pelletier M, et al. Neutrophil:lymphocyte ratio correlates with the uremic toxin indoxyl sulfate and predicts the risk of death in patients on Hemodialysis. Nephrol Dial Transpl. 2022;37:2528–37.
24. Neuen BL, Leather N, Greenwood AM, et al. Neutrophil-lymphocyte ratio predicts cardiovascular and all-cause mortality in Hemodialysis patients. Ren Fail. 2016;38:70–6.
25. Reddan DN, Klassen PS, Szczech LA, et al. White blood cells as a novel mortality predictor in haemodialysis patients. Nephrol Dial Transpl. 2003;18:1167–73.
26. Reuben DB, Ferrucci L, Wallace R, et al. The prognostic value of serum albumin in healthy older persons with low and high serum interleukin-6 (IL-6) levels. J Am Geriatr Soc. 2000;48:1404–7.
27. Lowrie EG, Lew NL. Death risk in Hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis. 1990;15:458–82.
28. Leavey SF, Strawderman RL, Jones CA, et al. Simple nutritional indicators as independent predictors of mortality in Hemodialysis patients. Am J Kidney Dis. 1998;31:997–1006.
29. Kaysen GA, Dubin JA, Müller HG, et al. Relationships among inflammation nutrition and physiologic mechanisms Establishing albumin levels in Hemodialysis patients. Kidney Int. 2002;61:2240–9.
30. Yeun JY, Kaysen GA. Factors influencing serum albumin in dialysis patients. Am J Kidney Dis. 1998;32:S118–25.
31. He HM, Zhang SC, He C, et al. Association between neutrophil percentage-to-albumin ratio and contrast-associated acute kidney injury in patients without chronic kidney disease undergoing percutaneous coronary intervention. J Cardiol. 2022;79:257–64.
32. Hu Z, Wang J, Xue Y, et al. The Neutrophil-to-Albumin ratio as a new predictor of All-Cause mortality in patients with heart failure. J Inflamm Res. 2022;15:701–13.
33. Yu Y, Liu Y, Ling X, et al. The neutrophil Percentage-to-Albumin ratio as a new predictor of All-Cause mortality in patients with cardiogenic shock. Biomed Res Int. 2020;2020:7458451.
34. Lan CC, Su WL, Yang MC, et al. Predictive role of neutrophil-percentage-to-albumin, neutrophil-to-lymphocyte and eosinophil-to-lymphocyte ratios for mortality in patients with COPD: evidence from NHANES 2011–2018. Respirology. 2023;28:1136–46.
35. Yu Y, Zhong Z, Yang W, et al. Neutrophil Percentage-to-Albumin ratio and risk of mortality in patients on peritoneal Dialysis. J Inflamm Res. 2023;16:6271–81.
36. Liao J, Wei D, Sun C, et al. Prognostic value of the combination of neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio and platelet-to-lymphocyte ratio on mortality in patients on maintenance Hemodialysis. BMC Nephrol. 2022;23:393.
37. Yang N, Yang K, Pan S, et al. Progress in the application of the neutrophil-to-lymphocyte ratio in dialysis-related complications. Ren Fail. 2023;45:2259996.

38. Zhang Y, Zhang A, Wei L, et al. A high platelet-to-lymphocyte ratio predicts all-cause mortality and cardiovascular mortality in maintenance Hemodialysis patients. Ren Fail. 2023;45:2258228.

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