BMC Nephrology

RESEARCH

Open Access

Inflammatory and nutritional indices for overall survival in Hemodialysis patients: a multicenter cohort study

Xinpan Chen[1†], Gang Wang[1†], Xiayan Yin[1], Wenhu Liu[1*], Hongdong Huang[1*] and Dishan Li[1*]

Abstract

Objective This study aimed to re-evaluate the prognostic value of inflammation and nutrition-related indices in a large multicenter cohort of hemodialysis patients from 138 dialysis centers in Beijing.

Methods This retrospective cohort study included 6,679 hemodialysis patients. Indices were calculated from routine laboratory parameters. Survival analyses included Kaplan-Meier curves and multivariate Cox models. C-index, receiver operating characteristic curves and decision curve analysis were used to evaluate the predictive ability of the different indicators.

Results All indicators (including Prognostic Nutritional Index [PNI], Lymphocyte-to-CRP Ratio [LCR], CRP-to-Albumin Ratio [CAR], Systemic Immune-Inflammation Index [SII], Platelet-to-Lymphocyte Ratio [PLR], and Neutrophil-to-Lymphocyte Ratio [NLR]) except for PLR were identified as independent predictors of OS (overall survival). Among these indicators, the PNI consistently demonstrated superior discriminatory ability in predicting outcomes among hemodialysis patients. Multivariate Cox regression analysis showed that the risk of mortality in hemodialysis decreased with an increase in PNI (adjusted HR 0.78, 95% CI: 0.75–0.82, $P < 0.01$). The optimal cut-off value for PNI was determined to be 42.3.

Conclusions PNI has demonstrated better reliability as a prognostic indicator for hemodialysis patients compared with LCR, CAR, SII, PLR and NLR. The efficient assessment of PNI effectively identifies high-risk individuals and highlights its significance as a valuable prognostic tool in clinical settings.

Keywords Inflammation, Nutrition, Prognostic nutritional index, Dialysis

†Xinpan Chen and Gang Wang contributed equally to this work and share first authorship.

*Correspondence:
Wenhu Liu
wenhuliu@mail.ccmu.edu.cn
Hongdong Huang
huanghd1126@126.com
Dishan Li
lidishan@vip.sina.com
[1]Department of Nephrology, Beijing Friendship Hospital, Capital Medical University, Beijing, China

Introduction

Hemodialysis, a life-sustaining therapy for patients with end-stage renal disease, poses significant challenges in prognostication due to complications such as anemia, malnutrition, and vascular calcification that are prevalent among patients undergoing this treatment [1, 2]. These complications contribute to increased morbidity and mortality rates by intricately linking with a persistent inflammatory state underlying adverse outcomes. The persistent state of inflammation observed in hemodialysis patients not only exacerbates the aforementioned complications but also contributes to protein-energy wasting, resulting in malnutrition [3]. Malnutrition is strongly associated with an increased risk of mortality among these patients. Therefore, close monitoring of both inflammatory and nutritional status is crucial for improving clinical management and patient outcomes.

Recent studies have shed light on the potential of various nutrition and inflammation-related factors as effective prognostic predictors in dialysis patients. Among these factors, markers of the systemic inflammatory response, such as the platelet-to-lymphocyte ratio (PLR) [4], lymphocyte-to-CRP ratio (LCR) [5], systemic immune-inflammation index (SII) [6], and neutrophil-to-lymphocyte ratio (NLR) [7], have emerged as key players in the progression and prognosis of hemodialysis patients. Furthermore, nutrition-related indicators, including the CRP-to-albumin ratio (CAR) and prognostic nutritional index (PNI) [8–11], have demonstrated their prognostic value in predicting outcomes for individuals undergoing hemodialysis. Notably, these indicators possess several advantages, such as simplicity, cost-effectiveness, widespread availability in most dialysis laboratories, and their confirmed value in predicting the survival of hemodialysis patients. However, to ensure their optimal utilization in clinical practice, it is imperative to determine which indicators hold the highest potential as prognosis predictors.

Therefore, the aim of this study was to assess and compare the predictive and prognostic roles of six biomarkers based on malnutrition and inflammation indicators in relation to overall survival (OS) among patients undergoing hemodialysis. Additionally, we conducted pooled analyses to identify the most promising indicators for overall survival in hemodialysis patients. By elucidating the prognostic value of these biomarkers, our aim is to contribute to the development of personalized therapeutic strategies and improve long-term outcomes for individuals undergoing hemodialysis.

Methods

Participants and study design

We conducted a retrospective multi-center cohort study involving individuals selected from the Beijing Hemodialysis Quality Control and Improvement Project. This project encompassed a total of 9196 individuals from 138 dialysis centers in Beijing between January 1, 2012, and December 31, 2019. The study's objective was to collect data for re-evaluating the prognostic value of inflammation- and nutrition- related indices in hemodialysis patients. For inclusion in the study, participants had to satisfy the following criteria: age ≥ 18 years and receiving hemodialysis three times a week for a minimum of 3 months. Exclusion criteria included: (1) hemodialysis duration less than 3 months; (2) prior peritoneal dialysis treatment; (3) organ transplantation history; (4) presence of malignant disease; (5) autoimmune or chronic/acute infectious disease; and (6) missing baseline data. The existence of acute or chronic infection was determined by admission diagnosis explicitly stating infection, such as pneumonia, or providing evidence of infection, such as detected bacteria or virus. After applying these criteria, a total of 6679 patients were eligible for enrollment in this study (Figure S1). The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Human Ethics Committee of Beijing Friendship Hospital, Capital Medical University (Number: BJFH-EC/2022-P2-385-01). Due to the retrospective nature of the study and the use of anonymized data, the requirement for informed consent was waived.

Clinical data

Clinical variables and potential confounders were chosen based on clinical guidelines and previous research. Only the data collected during the initial assessment after the start of hemodialysis were included. Baseline demographic data, as well as biochemical markers such as hemoglobin, albumin, platelet count, neutrophil count, lymphocyte count, C-reactive protein, creatinine, urea, calcium, parathormone, phosphorus, Fe (iron), ferritin and TIBC (total iron-binding capacity) were obtained within the first month of hemodialysis. To minimize measurement variability across different dialysis laboratories, the biochemical data were standardized before being recorded in the Beijing Hemodialysis Quality Control and Improvement Project database. The project database served as the source of data collection. The calculation formula of PNI, LCR, CAR, SII, NLR and PLR are shown in Table S7.

Outcome

The primary endpoint of interest was overall survival time. It was defined as the time span from the initiation of hemodialysis until death, transfer to another dialysis center, change to peritoneal dialysis, kidney transplantation, withdrawal from the study or end of follow-up (December 31, 2019).

Table 1 Demographic and clinical characteristics of the entire cohort and PNI stratification

Characteristic- *n* (%) or median (IQR)	Overall *n* = 6679	PNI-low *n* = 2596	PNI-high *n* = 4083	*P* value
Population characteristic				
Sex				
Female	3840 (57.5)	1464 (56.4)	2376 (58.2)	0.12
Male	2839 (42.5)	1132 (43.6)	1707 (41.8)	
Age	62.3 (51.3, 72.9)	66.5 (56.2, 76.2)	59.5 (48.3, 70.2)	< 0.01
Diabetes	2677 (40.1)	1171 (45.1)	1506 (36.9)	< 0.01
Hypertension	4252 (63.7)	1645 (63.4)	2607 (63.9)	0.71
Clinical characteristic- median (IQR)				
Hemoglobin (g/L)	97.0 (83.0, 111)	91.0 (79.0, 106)	100 (86.0, 114.0)	< 0.01
Platelets(10^9/L)	174 (138, 221)	168 (133, 219)	178 (141, 222)	< 0.01
Neutrophils (10^9/L)	4.24 (3.30, 5.41)	4.18 (3.21, 5.40)	4.26 (3.35, 5.42)	0.02
Lymphocytes (10^9/L)	1.18 (0.86, 1.57)	0.92 (0.63, 1.23)	1.36 (1.04, 1.74)	< 0.01
CRP (mg/L)	3.16 (1.00, 9.68)	3.44 (1.00, 12.8)	3.00 (1.10, 8.50)	0.01
Creatinine (umol/L)	784 (592, 970)	684 (512, 888)	848 (661, 1035)	< 0.01
Urea (mmol/L)	22.9 (17.4, 27.3)	21.7 (15.8, 26.5)	23.5 (18.5, 27.8)	< 0.01
Albumin (g/L)	37.9 (34.6, 41.4)	33.9 (31.3, 36.0)	39.9 (38.0, 43.0)	< 0.01
Calcium (mmol/L)	2.20 (2.10, 2.36)	2.15 (1.95, 2.32)	2.23 (2.12, 2.38)	< 0.01
Phosphorus (mmol/L)	1.68 (1.36, 2.15)	1.58 (1.27, 1.94)	1.75 (1.42, 2.22)	< 0.01
Parathormone (pg/ml)	183 (88.5, 328)	171 (84.2, 303)	192 (91.2, 346.7)	< 0.01
Fe (mmol/L)	10.1 (7.50, 13.9)	9.54 (6.98, 12.9)	10.50 (7.90, 14.4)	< 0.01
Ferritin (ng/ml)	229 (104, 450)	232 (108, 456)	228 (102, 447)	0.22
TIBC (umol/L)	41.3 (35.0, 49.1)	40.0 (33.2, 47.9)	42.2 (36.0, 49.9)	< 0.01
CAR	0.08 (0.03, 0.27)	0.10 (0.03, 0.41)	0.07 (0.03, 0.21)	< 0.01
LCR	3363 (1059, 10356)	2267 (545, 8116)	4262 (1552, 11500)	< 0.01
SII	618 (407, 1028)	785 (478, 1508)	558 (378, 840)	< 0.01
PLR	148 (107, 209)	186 (132, 285)	132 (98.8, 177)	< 0.01
NLR	3.54 (2.57, 5.25)	4.50 (3.16, 7.53)	3.13 (2.34, 4.24)	< 0.01

Data are shown as median (interquartile range) or number (%); IQR, interquartile range; The PNI-low group had an PNI < 42.3 and the PNI-high group had an PNI ≥ 42.3

Statistical analysis

Continuous variables with skewed distributions were presented as median (interquartile range) and compared using the Mann-Whitney test. Categorical data were expressed as numbers (percentages) and compared using Pearson's $\chi 2$ test. Spearman correlation analysis was used to identify linear relationships between indicators and variables. The multivariate Cox proportional hazards regression model was employed to assess the relationship between the indicators and overall survival. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test for time-to-event analysis. Restricted cubic splines were utilized to visualize the non-linear relationship between different indicators and HR. The optimal threshold for indicators was determined using the 'surv_cutpoint' formula in the 'survminer' R package, which employs an outcome-oriented approach to identify the cutoff value most closely associated with the outcome. The optimal prognostic indicator was determined through the utilization of prognostic receiver operator characteristic curve (ROC), decision curve analysis (DCA), and Harrell's concordance index (C-index).

The optimal cutoff value for PNI was determined to be 42.3 using an outcome-driven method. After determining the optimal cutoff value of PNI, participants were categorized into high- and low- PNI groups. Trend tests were performed by assigning a median value to each quartile of PNI, treating it as a continuous variable, and assessing statistical significance using the Wald test. Forest plots were employed to visualize the effects of PNI interactions with other variables on overall survival. Calibration curves were generated to assess the agreement between predicted and observed probabilities. The accuracy of the PNI in predicting outcomes was evaluated using the area under the ROC curve.

All statistical tests were two-sided, and a significance level of $P < 0.05$ was considered statistically significant. Statistical analyses were conducted using R software version 4.0.2 with the following packages: 'survminer', 'survival', 'rms', 'timeROC', 'forestplot', 'ISwR', 'ggDCA'.

Result

Baseline characteristics

In this cohort study, a total of 6679 hemodialysis patients were included. Baseline demographics indicated that the median age of the patients was 62.2 (51.3, 72.9) years, with 2839 (42.5%) being male. Among the enrolled patients, 2677 (40.1%) had diabetes and 4252 (63.7%) had hypertension (Table 1). During the median follow-up period of 30.8 months, a total of 2258 deaths were observed, resulting in an event rate of 115.1 events per 1,000 patient-years.

Multivariate cox regression analysis of mortality risk

Multivariate Cox regression survival analysis and Restricted Cubic Spline (RCS) found that compared with other indicators, PNI showed a good prognostic predictive ability in hemodialysis patients as a continuous variable or a categorical variable (Table 2; Fig. 1 and Figure S2). Moreover, the multivariate analysis indicated that, alongside PNI, factors such as age, diabetes, hypertension, hemoglobin, neutrophils, CRP, and creatinine significantly influenced mortality in the multivariate Cox regression model (Table S1). When PNI was used as a continuous variable (per SD), the risk of mortality in hemodialysis decreased as PNI increase (adjusted HR 0.78, 95% CI: 0.75–0.82, $P<0.01$). When PNI was used as a binary variable, compared with patients in the low PNI (<42.3) group, those with high PNI (≥42.3) had a reduced risk of mortality (adjusted HR 0.63, 95% CI: 0.58–0.69, $P<0.01$). When PNI was treated as a quartile variable, compared with patients in the first quartile (PNI<39.9) group, the risk of mortality in hemodialysis patients in the second, third, and fourth quartile groups decreased progressively (Quartile 2, adjusted HR 0.72, 95% CI: 0.64–0.80; Quartile 3, adjusted HR 0.62, 95% CI: 0.55–0.69; Quartile 4, adjusted HR 0.52, 95% CI: 0.46–0.59; all $P<0.01$; P for trend<0.01).

Optimal cut-off value of indicators

The cut-off value for the six indicators associated with mortality were determined using an outcome-oriented method based on Kaplan-Meier curves. The values were 42.3 for PNI, 1724.9 for LCR, 0.189 for CAR, 1456.9 for SII, 219.3 for PLR, and 4.89 for NLR (Figure S3 A-F). The survival curve results showed that the prognosis of patients with low PNI (<42.3) and low LCR (<1456.9) were worse than that of patients with high PNI (≥42.3) and high LCR (≥1456.9). Conversely, patients with high CAR (≥0.189), SII (≥1459.9), PLR (≥219.3) and NLR (≥4.89), had worse prognosis than those with low CAR (<0.189), SII (<1459.9), PLR (<219.3) and NLR (<4.89), respectively (Figure S4 A-F).

Comparison of indicators in Hemodialysis patients

Our C-index analysis indicated that PNI outperformed other indicators at 1, 3, 5, and 7 years, with values of 0.670 (95% CI 0.627,0.712), 0.633 (95% CI 0.612,0.653), 0.622 (95% CI 0.606,0.638) and 0.634 (95% CI 0.620,0.647) (Table S2 and Fig. 2A). The prognostic ROC curve consistently demonstrated that the area under the curve (AUC) of PNI was larger than that of other indicators (Fig. 2B). The DCA curves at 1, 3, 5, and 7 years demonstrated that within the threshold range, the PNI model yielded higher net benefits compared to the strategy of no prediction at specific decision thresholds. Additionally, across the entire threshold range, the DCA curves indicated that the PNI model had better net benefits than prediction models based on other indicators, highlighting its favorable clinical utility in predicting survival rates among hemodialysis patients (Fig. 2C).

Distribution, correlation, and prognostic analysis based on the PNI

The PNI levels were compared among different subgroups of the hemodialysis population based on sex, age, and comorbidities as diabetes and hypertension. Results indicated that young female (<65 years old) without diabetes had significantly higher PNI levels than elderly male (≥65 years old) with diabetes ($P<0.01$) (Figure S5A). Moreover, a Spearman correlation analysis was performed to investigate the association between PNI and various clinically relevant parameters in hemodialysis patients. The results revealed that PNI exhibited significant positive correlations with calcium, creatinine, urea, hemoglobin, platelets, neutrophil count, parathormone level, phosphorus level, iron level and TIBC while displaying a negative correlation with age and CRP. (Figure S5B).

Kaplan–Meier curves and log-rank test results revealed that the high PNI group exhibits a better prognosis compared with the low PNI group (Figure S4A). Table 1 presents a comparison of patient demographics and clinical characteristics between the low and high PNI groups. Briefly, patients in the low PNI group were associated with advanced age, diabetes, decreased levels of hemoglobin, platelets, neutrophils and lymphocytes; elevated CRP levels; as well as reduced creatinine, urea, albumin, calcium, phosphorus iron and TIBC levels. Additionally, the time-dependent ROC curve of PNI exhibited an AUC of 0.726, 0.648, 0.651 and 0.634 at intervals of 1, 3, 5 and 7 years respectively (Fig. 3A). The calibration curve demonstrated exceptional predictive ability of PNI in hemodialysis patients for up to seven years (Fig. 3B).

Stratification analysis

Stratified analyses were performed to evaluate the association between PNI and overall survival in different subgroups of hemodialysis patients (Fig. 4). High PNI consistently correlated with reduced mortality risk in all evaluated subgroups. Similar trends were observed in hemodialysis patients with Neutrophils<1.8 (10^9/L) and phosphorus<1.13 mmol/L, although these results did not achieve statistical significance ($P>0.05$). Interaction analysis identified age, CRP, and phosphorus level as effect modifiers influencing the PNI and mortality relationship (P for interaction<0.05). Notably, no significant difference in the risk of death was observed between patients with high PNI and low PNI in the age<30 group, CRP>15 group, and phosphorus<1.0 or >3.0 group (Figure S6). Additionally, the PNI and covariates were cross

Table 2 Relationships between different indicators and overall survival

	Crude model		Model A		Model B	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
PNI						
As continuous (per SD)	0.68 (0.66–0.71)	< 0.01	0.73 (0.70–0.76)	< 0.01	0.78 (0.75–0.82)	< 0.01
By PNI cut-off						
Low (< 42.3)	Ref		Ref		Ref	
High (≥ 42.3)	0.49 (0.45–0.53)	< 0.01	0.57 (0.52–0.62)	< 0.01	0.63 (0.58–0.69)	< 0.01
Interquartile						
Q1 (< 39.9)	Ref		Ref		Ref	
Q2 (39.9-43.95)	0.64 (0.57–0.71)	< 0.01	0.66 (0.59–0.73)	< 0.01	0.72 (0.64–0.80)	< 0.01
Q3 (43.95–47.95)	0.49 (0.44–0.55)	< 0.01	0.55 (0.49–0.61)	< 0.01	0.62 (0.55–0.69)	< 0.01
Q4 (≥ 47.95)	0.35 (0.31–0.40)	< 0.01	0.44 (0.39–0.50)	< 0.01	0.52 (0.46–0.59)	< 0.01
P for trend		< 0.01		< 0.01		< 0.01
LCR						
As continuous (per SD)	0.76 (0.70–0.82)	< 0.01	0.76 (0.71–0.82)	< 0.01	0.75 (0.70–0.81)	< 0.01
By LCR cut-off						
Low (< 1724.9)	Ref		Ref		Ref	
High (≥ 1724.9)	0.54 (0.50–0.59)	< 0.01	0.58 (0.53–0.63)	< 0.01	0.65 (0.60–0.71)	< 0.01
Interquartile						
Q1 (< 1059.7)	Ref		Ref		Ref	
Q2 (1059.7-3363.6)	0.72 (0.65–0.80)	< 0.01	0.70 (0.63–0.78)	< 0.01	0.77 (0.70–0.86)	< 0.01
Q3 (3363.6-10356.2)	0.53 (0.47–0.59)	< 0.01	0.56 (0.50–0.63)	< 0.01	0.67 (0.60–0.75)	< 0.01
Q4 (≥ 10356.2)	0.42 (0.37–0.48)	< 0.01	0.46 (0.41–0.52)	< 0.01	0.53 (0.47–0.60)	< 0.01
P for trend		< 0.01		< 0.01		< 0.01
CAR						
As continuous (per SD)	1.11 (1.09–1.13)	< 0.01	1.10 (1.08–1.12)	< 0.01	1.09 (1.07–1.12)	< 0.01
By CAR cut-off						
Low (< 0.189)	Ref		Ref		Ref	
High (≥ 0.189)	2.06 (1.90–2.24)	< 0.01	1.88 (1.73–2.04)	< 0.01	1.83 (1.68–1.99)	< 0.01
Interquartile						
Q1 (< 0.027)	Ref		Ref		Ref	
Q2 (0.027–0.083)	1.36 (1.18–1.56)	< 0.01	1.30 (1.13–1.49)	< 0.01	1.32 (1.15–1.52)	< 0.01
Q3 (0.083–0.274)	1.71 (1.50–1.96)	< 0.01	1.58 (1.38–1.81)	< 0.01	1.60 (1.40–1.84)	< 0.01
Q4 (≥ 0.274)	2.76 (2.43–3.14)	< 0.01	2.43 (2.14–2.76)	< 0.01	2.37 (2.08–2.71)	< 0.01
P for trend		< 0.01		< 0.01		< 0.01
SII						
As continuous (per SD)	1.06 (1.02–1.10)	0.01	1.06 (1.02–1.10)	< 0.01	1.06 (1.02–1.10)	< 0.01
By SII cut-off						
Low (< 1456.9)	Ref		Ref		Ref	
High (≥ 1456.9)	1.25 (1.11–1.40)	< 0.01	1.27 (1.13–1.43)	< 0.01	1.17 (1.04–1.32)	< 0.01
Interquartile						
Q1 (< 406.7)	Ref		Ref		Ref	
Q2 (406.7-617.9)	0.96 (0.85–1.07)	0.45	1.01 (0.90–1.13)	0.88	0.95 (0.84–1.07)	0.38
Q3 (617.9-1028.2)	0.99 (0.88–1.11)	0.86	1.05 (0.94–1.18)	0.37	0.99 (0.88–1.11)	0.90
Q4 (≥ 1028.2)	1.12 (1.00-1.26)	0.05	1.22 (1.08–1.37)	< 0.01	1.08 (0.96–1.21)	0.23
P for trend		0.06		< 0.01		0.19
PLR						
As continuous (per SD)	1.03 (0.99–1.06)	0.17	1.03 (0.99–1.06)	0.18	1.02 (0.98–1.05)	0.37
By PLR cut-off						
Low (< 219.3)	Ref		Ref		Ref	
High (≥ 219.3)	1.21 (1.10–1.34)	< 0.01	1.21 (1.10–1.34)	< 0.01	1.10 (1.00-1.22)	0.06
Interquartile						
Q1 (< 107.3)	Ref		Ref		Ref	
Q2 (107.3-147.8)	0.96 (0.86–1.08)	0.51	1.04 (0.93–1.17)	0.50	0.98 (0.87–1.10)	0.71

Table 2 (continued)

	Crude model		Model A		Model B	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Q3 (147.8-209.5)	0.96 (0.85–1.07)	0.45	1.04 (0.93–1.17)	0.48	0.98 (0.87–1.10)	0.71
Q4 (≥ 209.5)	1.11 (0.99–1.25)	0.07	1.18 (1.06–1.33)	< 0.01	1.03 (0.92–1.16)	0.60
P for trend		0.11		< 0.01		0.64
NLR						
As continuous (per SD)	1.06 (1.02–1.11)	< 0.01	1.06 (1.02–1.11)	< 0.01	1.07 (1.03–1.12)	< 0.01
By NLR cut-off						
Low (< 4.89)	Ref		Ref		Ref	
High (≥ 4.89)	1.23 (1.12–1.35)	< 0.01	1.24 (1.13–1.36)	< 0.01	1.19 (1.08–1.3)	< 0.01
Interquartile						
Q1 (< 2.57)	Ref		Ref		Ref	
Q2 (2.57–3.54)	1.02 (0.91–1.15)	0.71	1.09 (0.97–1.23)	0.13	1.03 (0.91–1.16)	0.64
Q3 (3.54–5.25)	1.07 (0.95–1.20)	0.28	1.14 (1.01–1.28)	0.03	1.08 (0.96–1.21)	0.20
Q4 (≥ 5.25)	1.22 (1.09–1.37)	< 0.01	1.30 (1.16–1.46)	< 0.01	1.20 (1.07–1.35)	< 0.01
P for trend		< 0.01		< 0.01		< 0.01

Crude model: unadjusted; Model A: adjusted for sex and age; Model B: adjusted for sex, age, diabetes, hypertension, hemoglobin level, lymphocyte count, platelet count, neutrophil count, albumin, creatinine, urea, calcium, phosphorus, parathormone, Fe, ferritin, TIBC and CRP, except for the indicator associated variable

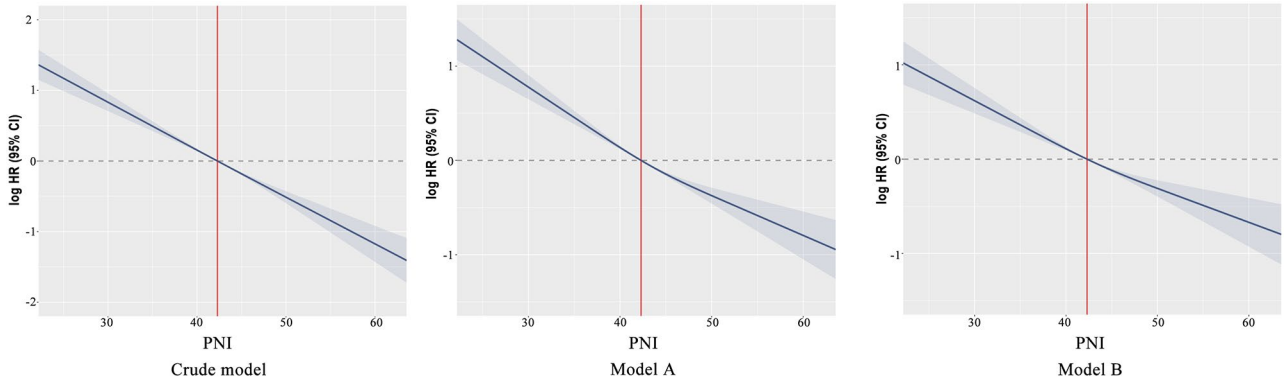

Fig. 1 Restricted cubic splines (RCSs) of PNI. Crude model: unadjusted; Model **A** adjusted for sex and age; Model **B** adjusted for sex, age, diabetes, hypertension, hemoglobin level, platelet count, neutrophil count, creatinine, urea, calcium, phosphorus, parathormone, Fe, ferritin, TIBC and CRP

classified to investigate the differential effects of each variant (Table S3). The results indicated that variables in an abnormal stage with low PNI levels had an additive effect, which exacerbated mortality risk. Kaplan-Meier curves further demonstrated the combined impact of PNI (high and low groups) and variables (normal and abnormal) on mortality in hemodialysis patients. Results indicated that those with a PNI of 42.3 or lower, aged ≥ 65 with diabetes and hypertension, as well as abnormal platelets and calcium levels had the poorest survival rates. (Figure S7).

Sensitive analysis and internal validation

To validate the robustness of PNI's prognostic value, sensitivity analyses and internal validation were performed (Table S4). After excluding patients who died within 6 months ($n = 6243$) of the initial assessment, the results demonstrated that PNI remained an independent prognostic factor (adjusted HR 0.79, 95% CI: 0.76–0.83, $P < 0.01$ for high PNI per SD) (Table S5). Then patients with CRP > 2 mg/L were also excluded ($n = 2540$), the results demonstrated that PNI were still an independent prognostic factor in hemodialysis patients after excluding CRP in acute phases (adjusted HR 0.76, 95% CI: 0.69–0.84, $P < 0.01$ for high PNI per SD). Subsequently, hemodialysis patients were randomly assigned to validation cohort A ($n = 4369$) and validation cohort B ($n = 2040$) in a 7:3 ratio based on computer-generated random numbers. Similarly, consistent findings were observed in both cohort A (adjusted HR 0.78, 95% CI: 0.74–0.82, $P < 0.01$ for high PNI per SD) and cohort B (adjusted HR 0.79, 95% CI: 0.73–0.86, $P < 0.01$ for high PNI per SD) (Table S5). Furthermore, Kaplan-Meier curves demonstrated that hemodialysis patients with high PNI had significantly better prognosis in sensitivity analysis and internal validation (Figure S8 A-D).

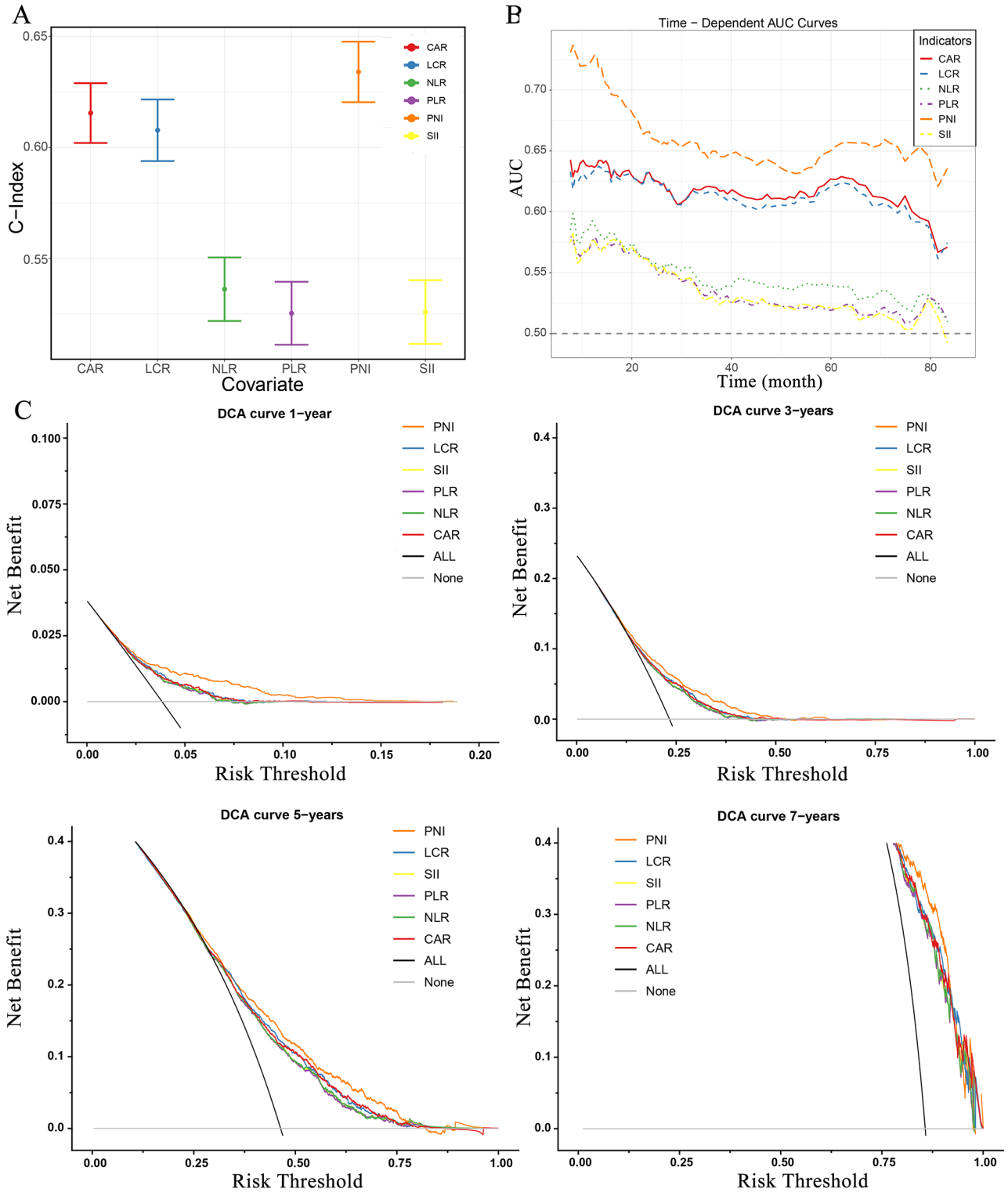

Fig. 2 C-index, prognostic ROC and DCA curve of different indicators. (**A**) 7-years C-index of six nutrition/inflammation indicators. (**B**) prognostic ROC. (**C**) DCA curve. NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; LCR: Lymphocyte-to-C-Reactive Protein Ratio; SII: Systemic Immune-Inflammatory Index; PNI: Prognostic Nutritional Index; ROC, Receiver Operating Characteristic Curve; DCA, Decision Curve Analysis

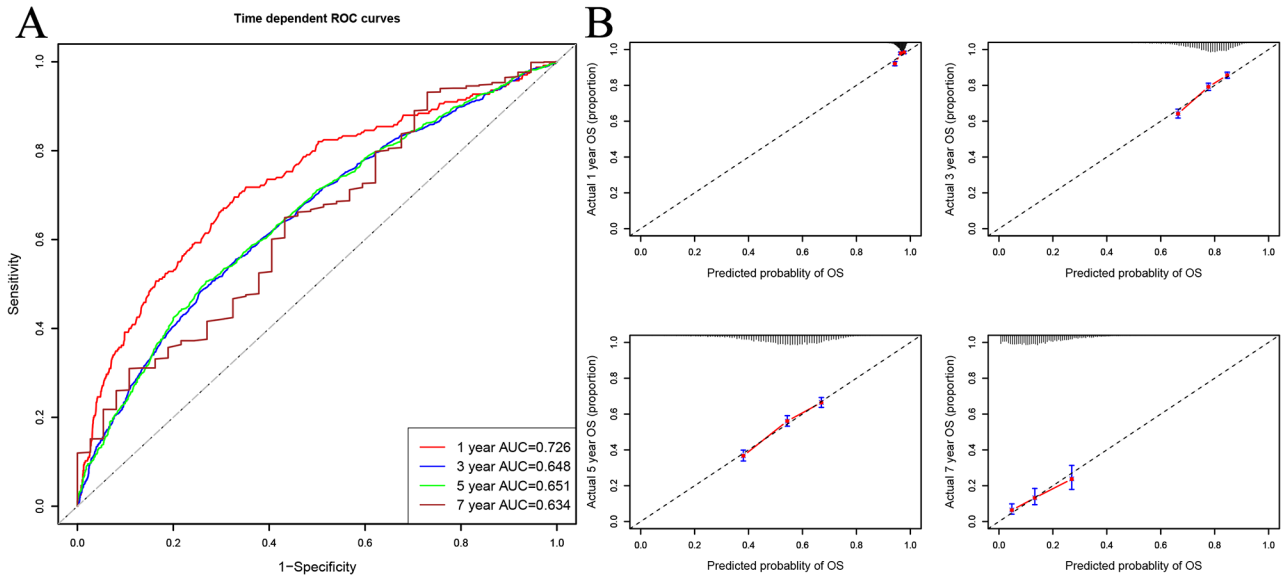

Fig. 3 ROC curves and Calibration curves of PNI. (**A**) The AUCs for 1, 3, 5, and 7 years were calculated to be 0.726, 0.648, 0.651, and 0.634 respectively. (**B**) Calibration curves of PNI for 1, 3, 5, and 7 years. AUC, area under the curve

Discussion

Accumulating evidence supports the prognostic utility of inflammatory and nutritional biomarkers in hemodialysis populations, yet the optimal indicator remains elusive. Our study utilized a large cohort to systematically evaluate six candidate indices. Consistent with prior research, univariate and multivariate analyses identified PNI, LCR, CAR, SII and NLR as independent prognostic factors for all-cause mortality, except for PLR (Table S6). The PNI showed the highest discriminatory ability among evaluated indicators in predicting outcomes of hemodialysis patients. Furthermore, both continuous and categorical analyses of PNI revealed strong prognostic value, with each one-unit increase or standard deviation increase in PNI, there was a 0.956-fold or 0.78-fold decrease in mortality risk among hemodialysis patients.

The composite indices integrate albumin, platelet counts, neutrophils, lymphocytes, and CRP levels to reflect multifaceted inflammatory and nutritional status. Platelets actively participate in immunological processes through releasing pro-inflammatory mediators such as platelet-derived prostaglandin E2 and C-type lectin-like receptor 2 [12], but mean platelet volume (MPV), rather than platelet counts, has been associated with mortality in hemodialysis patients [13]. Neutrophils play a crucial role in the host's defense against bacterial and viral infections [14], exhibit impaired function in uremia, increasing infection-related mortality. Lymphocytes are important in the cytotoxic immune response with lower counts linked to higher mortality risk [15]. CRP has proven to be a valuable biomarker of inflammation and infection, independently predicts mortality in hemodialysis patients and correlates with coronary artery disease and cerebrovascular accident [16]. Our findings confirm significant association between albumin, neutrophils, lymphocytes and CRP levels and mortality among hemodialysis patients, while platelet counts showed no correlation. This explains why PLR failed to emerge as an independent prognostic indicator, which is consistent with the findings reported by Mayne et al. [17].

Inflammation, immunity, and malnutrition are intricately intertwined. Chronic inflammation in hemodialysis patients often coexists with immune dysfunction and malnutrition, while malnutrition exacerbates immune deficiency and infection susceptibility. Protein-energy wasting (PEW) is a prevalent phenomenon among patients with chronic diseases, particularly those undergoing hemodialysis, and it has been linked to elevated mortality rates [18]. Elevated concentrations of uremic toxins and persistent inflammation contribute to the development of PEW, leading to reduced nutrient intake, increased resting energy expenditure, and muscle atrophy [19]. Albumin reflects the nutritional status and is confounded by systemic inflammation in dialysis patients [20]. Previous studies confirm its predictive value for all-cause, cardiovascular, and infection-related mortality in both PD and HD patients [21]. A recent study involving 787 hemodialysis patients has demonstrated that higher CAR was significantly associated with a higher mortality risk in the first six months of HD [9]. Our study also identified that CAR were independent prognostic biomarkers in hemodialysis patients. The PNI, calculated as serum albumin + 0.05 × lymphocyte count, also emerged as a robust mortality predictor. Both PNI and CAR integrate nutritional and inflammatory markers, potentially explaining their superior performance over single

Variables	No. of patients	HR (95%CI)	P value	P for interaction
Age				**0.045**
>65	1306/2843	0.67(0.60,0.75)	<0.001	
<=65	952/3836	0.56(0.49,0.65)	<0.001	
Sex				**0.085**
Male	1133/2839	0.67(0.59,0.76)	<0.001	
Famale	1125/3840	0.60(0.53,0.68)	<0.001	
Diabetes				**0.563**
Yes	1124/2677	0.61(0.54,0.70)	<0.001	
No	1134/4002	0.66(0.58,0.75)	<0.001	
Hypertension				**0.229**
Yes	1574/4252	0.63(0.57,0.71)	<0.001	
No	684/2427	0.63(0.53,0.74)	<0.001	
Hemoglobin				**0.898**
<100	1241/3667	0.63(0.56,0.71)	<0.001	
100−120	731/2138	0.64(0.55,0.75)	<0.001	
>120	286/874	0.62(0.48,0.79)	<0.001	
Platelets				**0.108**
<125	435/1149	0.63(0.52,0.77)	<0.001	
125−350	1774/5394	0.64(0.58,0.71)	<0.001	
>350	49/136	0.35(0.17,0.73)	0.005	
Neutrophils				**0.812**
<1.8	54/126	0.71(0.36,1.42)	0.335	
1.8−6.3	1877/5597	0.63(0.57,0.70)	<0.001	
>6.3	327/956	0.64(0.50,0.81)	<0.001	
CRP				**0.013**
>=10	841/1636	0.81(0.70,0.93)	0.004	
<10	1417/5043	0.57(0.51,0.63)	<0.001	
Calcium				**0.724**
<2.11	658/1882	0.62(0.53,0.74)	<0.001	
2.11−2.52	1324/4000	0.66(0.59,0.74)	<0.001	
>2.52	276/797	0.56(0.43,0.74)	<0.001	
Phosphorus				**0.04**
<1.13	306/700	0.90(0.71,1.16)	0.425	
1.13−1.78	1129/3150	0.61(0.54,0.69)	<0.001	
>1.78	823/2829	0.61(0.53,0.71)	<0.001	
Parathormone				**0.439**
<150	1067/2811	0.59(0.51,0.67)	<0.001	
150−300	633/1952	0.63(0.53,0.74)	<0.001	
>300	558/1916	0.75(0.63,0.90)	0.001	
Ferritin				**0.627**
<200	925/3007	0.58(0.50,0.66)	<0.001	
200−500	747/2241	0.66(0.56,0.77)	<0.001	
>500	586/1431	0.67(0.56,0.80)	<0.001	
TIBC				**0.921**
<50	1700/5124	0.63(0.57,0.70)	<0.001	
50−77	382/1180	0.69(0.56,0.86)	0.001	
>77	176/375	0.68(0.49,0.94)	0.02	

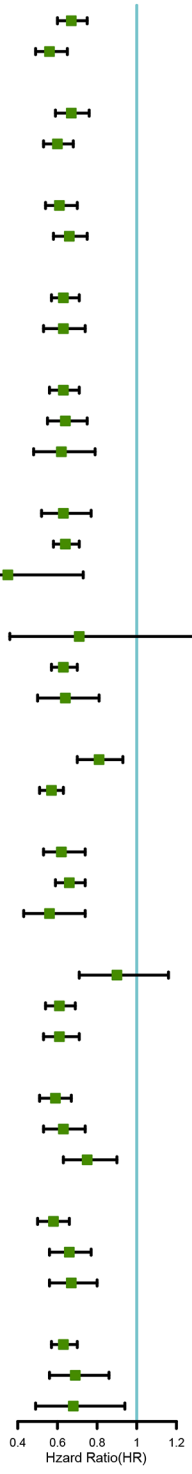

Fig. 4 The subgroup analysis of PNI in hemodialysis patients. The model of adjusted variables: sex, age, diabetes, hypertension, hemoglobin level, platelet count, neutrophil count, creatinine, urea, calcium, phosphorus, parathormone, Fe, ferritin, TIBC and CRP, except for the stratifying variable

biomarkers. While PNI demonstrated numerically higher discrimination across multiple metrics and greater net benefit in decision curve analysis (DCA), the partial overlap in confidence intervals between PNI and CAR/LCR suggests that the observed differences may not reach statistical significance.

In recent years, the utility of PNI as a prognostic indicator for overall survival has been validated across diverse clinical populations, including oncology, cardiovascular disease, decompensated cirrhosis, diabetic nephropathy, and dialysis cohorts [22–25]. Consistent with previous studies, our RCS model revealed a linear-like relationship between PNI and all-cause mortality in hemodialysis patients, characterized by a smooth curve approximating linearity, which underscores its robust prognostic value. Although PNI has emerged as a promising biomarker, its optimal cutoff value remains context-dependent, with previous studies reporting thresholds ranging widely from 30 to 45 [26–30]. In our study, we have established a specific cut-off value of 42.3 for PNI using an outcome-oriented method. Our findings indicate that hemodialysis patients with a PNI below this threshold are at higher risk of mortality. Patients with low PNI levels exhibit elevated CRP levels, advanced age, diabetes mellitus, and decreased hemoglobin, platelet count, neutrophil count and lymphocyte count, all of which are associated with poor outcomes. Furthermore, a stratified analysis conducted in the present study demonstrates that PNI possesses prognostic value when used in conjunction with various clinical parameters. Low PNI patients exhibiting abnormal clinical parameters consistently exhibit an additive effect on increasing mortality risk. Interaction analysis has identified that age, CRP level, and phosphorus level acted as effect modifiers influencing the relationship between PNI and risk of death. The prognostic utility of PNI may be limited in patients younger than 30 years old or with CRP levels over 15 mg/L or phosphorus levels below 1.0 mmol/L or above 3.0 mmol/L, indicating that PNI may not be suitable for clinical use in such patients.

This study represents one of the largest investigations to date evaluating the prognostic utility of inflammatory and nutritional biomarkers in hemodialysis populations. However, it is important to acknowledge several limitations inherent in our study. Firstly, we were unable to analyze other conventional indicators such as GNRI (geriatric nutritional risk index), NRI (nutritional risk index), and COUNT score (controlling nutritional status score) due to the unavailability of specific data in the database. In future studies, incorporating additional parameters such as TGF-β would contribute to a more comprehensive evaluation of inflammation. Secondly, it would be valuable to evaluate whether changes in PNI values during hemodialysis treatment, beyond the baseline measurement, are linked with clinical outcomes. This inquiry would offer insights into the prognostic significance of PNI at different time-points. Moreover, it is imperative to acknowledge that the current study was a retrospective analysis conducted across multiple centers, which introduces the possibility of unidentified confounders that may have influenced the obtained data and introduced bias. To address this limitation, well-designed prospective trials are warranted to mitigate confounding factors and provide stronger evidence. Lastly, it is imperative to conduct external validation of our findings using large sample sizes from diverse geographical regions in order to ensure the generalizability of our results to all patients undergoing hemodialysis.

In conclusion, despite the limitations, our study provides significant insights into the prognostic value of various inflammatory-nutrition biomarkers. Among all the indicators compared, PNI exhibited a better performance in predicting prognosis. The evaluation of PNI could effectively identify high-risk patients and serve as a valuable prognostic marker in clinical practice.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-025-04121-3.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Acknowledgements

All authors would like to thank Kangping Zhang, PhD from Capital Medical University for editing the language of a draft of this manuscript.

Author contributions

X.C.: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing. G.W.: Conceptualization; Formal analysis; Writing – original draft; Supervision. X.Y.: Data curation; Methodology; Validation. W.L.: Formal analysis; Validation; Visualization; Writing – review & editing. H.H.: Data curation; Supervision; Validation; Writing – review & editing. D.L.: Conceptualization; Methodology; Writing – review & editing; Supervision. All authors reviewed the manuscript.

Funding

No funding was received for this study.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Human Ethics Committee of Beijing Friendship Hospital, Capital Medical University (Number: BJFH-EC/2022-P2-385-01). The privacy and personally identifiable information of the patients in this study were protected. This study did not identify any patients, and the research project did not involve personal privacy and commercial

interests. Thus, the need for informed consent was waived due to the retrospective nature of the study and the use of anonymized data.

Competing interests
The authors declare no competing interests.

Received: 16 July 2024 / Accepted: 11 April 2025
Published online: 07 May 2025

References

1. Sahathevan S, Khor BH, Ng HM, Gafor AHA, Mat Daud ZA, Mafra D et al. Understanding development of malnutrition in Hemodialysis patients: A narrative review. Nutrients 2020;12:3147.
2. Ekdahl KN, Soveri I, Hilborn J, Fellstrom B, Nilsson B. Cardiovascular disease in haemodialysis: role of the intravascular innate immune system. Nat Rev Nephrol. 2017;13:285–96.
3. Cobo G, Lindholm B, Stenvinkel P. Chronic inflammation in end-stage renal disease and dialysis. Nephrol Dial Transpl. 2018;33:iii35–40.
4. Zhang J, Lu X, Wang S, Li H. High Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio Are Associated with Poor Survival in Patients with Hemodialysis. Biomed Res Int. 2021; 2021:9958081.
5. Chen X, Guo W, Diao Z, Huang H, Liu W. Lymphocyte-to-C reactive protein ratio as novel inflammatory marker for predicting outcomes in Hemodialysis patients: A multicenter observational study. Front Immunol. 2023;14:1101222.
6. Lai W, Xie Y, Zhao X, Xu X, Yu S, Lu H, et al. Elevated systemic immune inflammation level increases the risk of total and cause-specific mortality among patients with chronic kidney disease: a large multi-center longitudinal study. Inflamm Res. 2023;72:149–58.
7. Liao J, Wei D, Sun C, Yang Y, Wei Y, Liu X. 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.
8. Hwang JC, Jiang MY, Lu YH, Wang CT. Precedent fluctuation of serum hs-CRP to albumin ratios and mortality risk of clinically stable Hemodialysis patients. PLoS ONE. 2015;10:e0120266.
9. Sant'Ana M, Gameiro J, Costa C, Branco C, Marques da Silva B, Peres N, et al. C-reactive protein-to-albumin ratio and six-month mortality in incident Hemodialysis patients. Ren Fail. 2023;45:2182615.
10. Barutcu Atas D, Tugcu M, Asicioglu E, Velioglu A, Arikan H, Koc M, et al. Prognostic nutritional index is a predictor of mortality in elderly patients with chronic kidney disease. Int Urol Nephrol. 2022;54:1155–62.
11. Kitabayashi K, Yamamoto S, Narita I. Association of the nutritional risk index for Japanese Hemodialysis with mortality and dietary nutritional intake in patients undergoing Hemodialysis during long-term hospitalization. Clin Exp Nephrol. 2022;26:1200–7.
12. Ludwig N, Hilger A, Zarbock A, Rossaint J. Platelets at the crossroads of pro-inflammatory and resolution pathways during inflammation. Cells 2022;11:1957.
13. Kim S, Molnar MZ, Fonarow GC, Streja E, Wang J, Gillen DL, et al. Mean platelet volume and mortality risk in a National incident Hemodialysis cohort. Int J Cardiol. 2016;220:862–70.
14. Talal S, Mona K, Karem A, Yaniv L, Reut HM, Ariel S, et al. Neutrophil degranulation and severely impaired extracellular trap formation at the basis of susceptibility to infections of Hemodialysis patients. BMC Med. 2022;20:364.
15. Reddan DN, Klassen PS, Szczech LA, Coladonato JA, O'Shea S, Owen WF Jr., et al. White blood cells as a novel mortality predictor in haemodialysis patients. Nephrol Dial Transpl. 2003;18:1167–73.
16. Bazeley J, Bieber B, Li Y, Morgenstern H, de Sequera P, Combe C, et al. C-reactive protein and prediction of 1-year mortality in prevalent Hemodialysis patients. Clin J Am Soc Nephrol. 2011;6:2452–61.
17. Mayne KJ, Lees JS, Rutherford E, Thomson PC, Traynor JP, Dey V, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios: associations with mortality in a haemodialysis cohort. Clin Kidney J. 2023;16:512–20.
18. Rahman T, Khor BH, Sahathevan S, Kaur D, Latifi E, Afroz M et al. Protein energy wasting in a cohort of maintenance Hemodialysis patients in Dhaka, Bangladesh. Nutrients 2022;14:1469.
19. Graterol Torres F, Molina M, Soler-Majoral J, Romero-Gonzalez G, Rodriguez Chitiva N, Troya-Saborido M et al. Evolving Concepts on Inflammatory Biomarkers and Malnutrition in Chronic Kidney Disease. Nutrients. 2022;14.
20. Lai KJ, Hsieh YP, Chiu PF, Lin PR. Association of Albumin and Globulin with Mortality Risk in Incident Peritoneal Dialysis Patients. Nutrients. 2022;14.
21. Mehrotra R, Duong U, Jiwakanon S, Kovesdy CP, Moran J, Kopple JD, et al. Serum albumin as a predictor of mortality in peritoneal dialysis: comparisons with Hemodialysis. Am J Kidney Dis. 2011;58:418–28.
22. Zhang J, Xiao X, Wu Y, Yang J, Zou Y, Zhao Y et al. Prognostic nutritional index as a predictor of diabetic nephropathy progression. Nutrients 2022;14:3634.
23. Kuo S, Yang CT, Chen HY, Ou HT. Valuing health States of people with type 2 diabetes: analyses of the nationwide representative linked databases. J Diabetes Investig. 2021;12:1749–58.
24. Ma S, Zhang B, Lu T, Li D, Li T, Shen Z, et al. Value of the prognostic nutritional index (PNI) in patients with newly diagnosed, CD5-positive diffuse large B-cell lymphoma: A multicenter retrospective study of the Huaihai lymphoma working group. Cancer. 2022;128:3487–94.
25. Xie Y, He C, Wang W. Prognostic nutritional index: A potential biomarker for predicting the prognosis of decompensated liver cirrhosis. Front Nutr. 2022;9:1092059.
26. Liu X, Shao S, Zhang N, Wu M, Liu L, Duan H, et al. Predictive role of sampling-time specific prognostic nutritional index cut-off values for intravenous Immunoglobulin resistance and cardiovascular complications in Kawasaki disease. Int Immunopharmacol. 2022;110:108986.
27. Kubota K, Ito R, Narita N, Tanaka Y, Furudate K, Akiyama N, et al. Utility of prognostic nutritional index and systemic immune-inflammation index in oral cancer treatment. BMC Cancer. 2022;22:368.
28. Bruixola G, Caballero J, Papaccio F, Petrillo A, Iranzo A, Civera M, et al. Prognostic nutritional index as an independent prognostic factor in locoregionally advanced squamous cell head and neck cancer. ESMO Open. 2018;3:e000425.
29. Oe S, Togawa D, Yamato Y, Hasegawa T, Yoshida G, Kobayashi S, et al. Preoperative age and prognostic nutritional index are useful factors for evaluating postoperative delirium among patients with adult spinal deformity. Spine (Phila Pa 1976). 2019;44:472–8.
30. Kalayci T, Kartal M. Significance of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, serum albumin and prognostic nutritional index as predictors of morbidity in super-elderly patients operated on for acute appendicitis. Eur Rev Med Pharmacol Sci. 2022;26:820–7.

Publisher's note