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The relationship between the prognostic nutritional index and new-onset pneumonia in peritoneal dialysis patients

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Abstract

Purpose As an indicator of nutrition and immunity, the prognostic value of the prognostic nutritional index (PNI) has been confirmed in various diseases. However, the relationship between PNI and the incidence of pneumonia in peritoneal dialysis (PD) patients remains unknown. The purpose of this study was to investigate the relationship between PNI and new-onset pneumonia in patients undergoing PD.

Methods Thousand two hundred and nighty eight patients were enrolled in this multicenter retrospective study from February 1, 2010, to February 28, 2020. A total of 899 patients were included in the final statistical analysis. The patients were stratified into two groups by PNI quartiles. The primary endpoint was a new-onset pneumonia event. Cox regression model analysis was used to explore the association between PNI and the first occurrence of pneumonia.

Results During a mean follow-up of 41.43 months, 147 patients developed new-onset pneumonia. Kaplan–Meier survival curves showed a significant difference in the incidence of the first presentation of pneumonia between the two groups, that patients in the low PNI group had a higher risk of pneumonia ($P=0.016$). By adjusting for demographic parameters, comorbidities, and laboratory indicators, the Cox regression model showed that the high PNI group had less risk compared to the low PNI group (HR 0.479 95% CI 0.297–0.772, $P=0.003$). There were no interactions in the subgroups as follows: diabetes, hypertension, age, and sex.

Conclusions Low PNI levels were independently associated with the first occurrence of pneumonia in PD patients. PNI was an independent predictor of new-onset pneumonia in PD patients.

Keywords Prognostic nutrition index · Peritoneal dialysis · Pneumonia · Chronic kidney disease

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Introduction

Patients with chronic kidney disease were more susceptible to infections [1–3]. Infections were the second most common cause of hospitalization and death, and about one in a quarter of infection-related deaths were due to pulmonary disease in the National Kidney Registry study [4]. Some studies showed the cumulative probability of pneumonia hospitalization was 36% at 5 years in dialysis patients. The mortality after pulmonary infectious was 14–16-fold higher in dialysis patients compared with the normal population [5, 6]. Long-term respiratory tract infection is prone to cardiovascular events, such as myocardial infarction, which poses a huge burden on the health care system [7].

In patients with hemodialysis, good nutritional status had a protective effect against pulmonary infection and was associated with improved survival [8]. On the contrary, there is a close relationship between malnutrition and inflammation, chronic malnutrition leads to compromised immune function and infections [9]. Protein-energy depletion (PEW), characterized by significantly low serum albumin levels, inflammation, and oxidative stress, is common in patients with chronic kidney disease [10]. PEW is associated with significantly higher mortality and lower quality of life [11]. Prognostic nutritional index (PNI), combined with serum albumin and lymphocyte count, may be an excellent PEW biomarker [12]. The low PNI was associated with CVD mortality in PD patients [13]. It is not clear whether PNI is associated with the occurrence of pneumonia in patients with PD.

Methods

Participants

The cohort included 1298 patients who underwent peritoneal dialysis between February 1, 2010, and February 28, 2020, from 3 peritoneal dialysis centers, and followed until June 1, 2020. Patients aged < 18 years or >80 years and who lacked albumin or lymphocyte count data were excluded. The study proposal was conducted in accordance with the ethical principles of the Declaration of Helsinki and approved by the Institutional Review Board of the Sixth Hospital of Sun Yat-sen University (No. 2021SLYEC-177). Written informed consent was not required for this study because of the retrospectively collected medical records available in the hospitals.

Data collection

All data were collected within 3 months after starting peritoneal dialysis. Demographic data included age, gender, body mass index (BMI), smoking and drinking history, underlying diseases, such as diabetes, hypertension, and cardiovascular disease. PNI was calculated using the formula $PNI = (10 \times Alb\ g/dL) + (0.005 \times total\ lymphocyte\ counts/mm^3)$ [13]. BMI was calculated as body weight in kilograms divided by height in meters squared. The weight and height determined at admission were used to calculate BMI. The diagnosis of a history of diabetes was based on the diagnostic criteria of the American Diabetes Association [14]. Hypertension was recorded if the patient was taking antihypertensive medication or had two blood pressure measurements ≥ 140/90 mmHg [15]. Other histories of diseases were recorded according to the first page of the patient's medical record. The definition of pneumonia mainly depends on discharge diagnosis. The diagnosis of pneumonia is defined by a professional respiratory physician based on the patient's symptoms, such as cough, dyspnea, and fever, the results of laboratory tests, and the presence of a new infiltrate on the chest X-ray or CT [16].

Outcomes

The primary outcome of this study was the first occurrence of pneumonia. The follow-up endpoint was any of the following: death, transfer to hemodialysis, transfer to another center, transfer to kidney transplant, or censoring on June 1, 2020.

Statistical analysis

Patients were divided into two groups based on the quartiles of PNI. The first quartile PNI is low PNI (PNI ≤ 36.1), and the other three quartiles PNI are high PNI (PNI > 36.1) [13]. Continuous variables conforming to a normal distribution were expressed as mean ± standard deviation, and continuous variables conforming to a skewed distribution were expressed as median (25th–75th percentile). Categorical variables were expressed in terms of numbers (percentiles). The difference between the PNI groups was tested by *t* test, Chi-squared, or the nonparametric Mann–Whitney test. Univariate Cox regression explored possible factors associated with the onset of first pneumonia. Cox proportional risk regression model was used to test the relationship between PNI and new pneumonia: model 1: BMI and age, model 2: model 1 plus comorbid conditions and history of smoking and drinking, model 3: model 2 plus laboratory parameters. The Kaplan–Meier curve was used to examine

the difference in the risk of new-onset pneumonia between the two PNI groups during follow-up. The log-rank test was used to evaluate the differences. Spearman correlation analysis was used to explore the correlation between PNI and other nutrition-related indicators and other indicators. The forest map was used to show subgroup analysis, comparing whether there are interactions. The statistical analysis was done by SPSS25.0 and GraphPad Prism (version 8.0.2). *P* value < 0.05 was considered statistically significant.

Results

Participants

A total of 1298 patients were collected in three centers, of which 399 were excluded for the following reasons: significant data were absent from the study ($n=377$), age younger than 18 years or older than 80 years ($n=22$). 899 patients were ultimately included in the study. 147 patients developed pneumonia. (Fig. 1). Baseline demographic data and laboratory indicators of patients are demonstrated in Table 1. Of the 899 patients, the median age was 59 (47–67) years; 516 (57.4%) patients were men; 259 (28.8%) had diabetes, and 615 (68.4%) had hypertension. The median PNI level at baseline was 40.6 (36.8–43.6) for all patients. The median follow-up time was 41.13 months and the maximum follow-up time was 122 months. Patients in the high PNI group had a lower incidence of diabetes. There was no significant difference in the incidence of previous cardiovascular disease and hypertension. The levels of white blood cells, triglycerides, hemoglobin, serum calcium, phosphorus, and potassium in patients with low PNI were lower than those in patients with high PNI. The levels of platelets and HDL were higher in the low PNI group (Table 1).

Correlations between baseline PNI and clinical parameters

The Spearman correlation coefficients demonstrated that PNI values were significantly positively correlated with BMI ($r=0.077$), WBC ($r=0.111$), RBC ($r=0.190$), hemoglobin ($r=0.208$) and triglyceride ($r=0.207$). Meanwhile, PNI was negatively correlated with age ($r=-0.204$) and HDL ($r=-0.091$). The correlation between PNI and cholesterol was not statistically significant (Table 2).

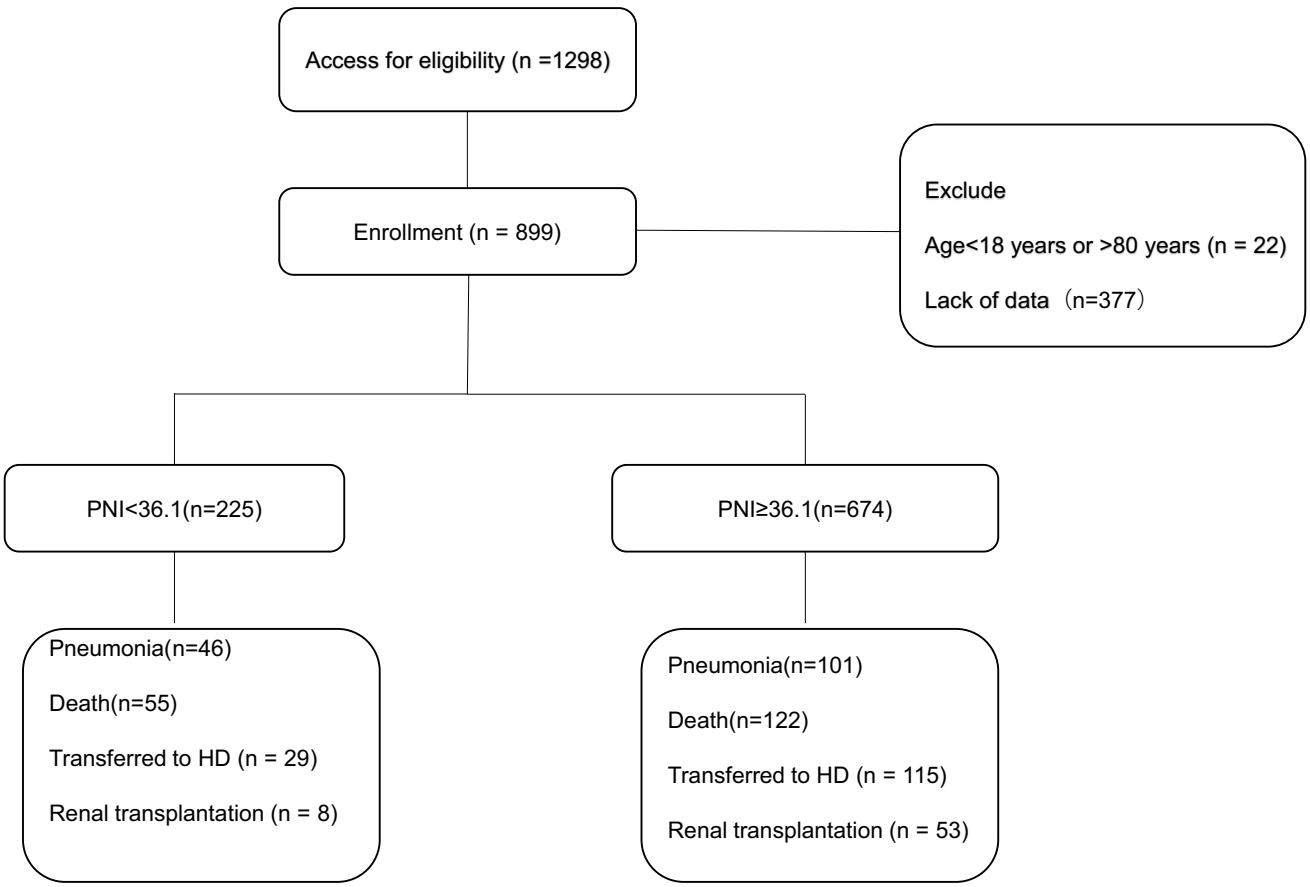

Fig.1 Flowchart of participants enrollment and outcomes. *HD* hemodialysis

Table 1 Demographic and baseline clinical data

Variables	Total ($n=899$)	PNI < 36.1 ($n=225$)	PNI ≥ 36.1 ($n=674$)	P value
Demographics				
Age (years)	59 (47–67)	63 (56–69)	56 (43–66)	< 0.001
Gender (male%)	516 (57.4%)	127 (56.4%)	389 (57.7%)	0.739
BMI (kg/m^2)	22.3 (20.1–24.8)	22.1 (20.3–24.4)	22.5 (20. 5–24.6)	0.164
Smoking history	97 (10.8%)	20 (8.9%)	77 (11.4%)	0.289
Drinking history	32 (3.6%)	5 (2.2%)	27 (4%)	0.211
Comorbid				
Diabetes (%)	259 (28.8%)	90 (40.0%)	169 (25.1%)	< 0.001
Hypertension (%)	615 (68.4%)	157 (69.8%)	458 (68.0%)	0.610
CVD (%)	132 (14.7%)	37 (16.4%)	95 (14.5%)	0.389
Laboratory variables				
Leukocyte (10^9/L)	6.2 (5.2–7.7)	6.1 (5.0–7.6)	6.3 (5.2–7.8)	0.030
Creatinine (mg/dL)	592.0 (449.3–815.3)	502.0 (427.0–652.0)	644.0 (496.0–850.0)	0.086
Blood urea nitrogen (mg/dL)	16.3 (12.3–21.5)	15.58 (12.3–19.1)	16.92 (12.4–22.7)	0.833
Hemoglobin (g/L)	100.5 (86.0–114.3)	93.0 (84.0–109.0)	101.0 (87.0–117.0)	0.005
Platelet (10^9/L)	221.0 (177.0–272.0)	254.0 (179.0–307.0)	214.5 (177.0–262.8)	< 0.001
Total cholesterol (mmol/L)	4.5 (3.9–5.3)	4.5 (3.8–5.7)	4.6 (3.9–5.3)	0.384
Triglycerides (mmol/L)	1.5 (1.0–2.0)	1.2 (0.9–1.5)	1.5 (1.1–2.1)	< 0.001
HDL (mmol/L)	1.0 (0.8–1.2)	1.1 (0.9–1.4)	1.0 (0.8–1.2)	0.028
Phosphorus (mmol/L)	1.4 (1.1–1.8)	1.2 (1.0–1.6)	1.4 (1.1–1.8)	< 0.001
Calcium (mmol/L)	2.2 (2.0–2.3)	2.0 (1.9–2.2)	2.2 (2.0–2.3)	< 0.001
Potassium (mmol/L)	3.9 (3.4–4.5)	3.6 (3.1–4.1)	4.0 (3.5–4.5)	0.006
RRF (mL/min)	2.9 (1.3–6.0)	2.4 (0.9–5.4)	3.3 (1.5–6.1)	0.090
PNI	40.6 (36.8–43.6)	32.8 (30.5–34.8)	42 (39.3–44.7)	< 0.001

BMI body mass index, *CVD* Cardiovascular disease, *RRF* residual renal function, *HDL* high density lipoprotein, *PNI* prognostic nutritional index

Table 2 Correlations between baseline PNI and clinical parameters

Factors	Spearman r	P
Age (years)	−0.204	< 0.001
BMI (kg/m^2)	0.077	0.021
WBC (10^9/L)	0.111	0.001
RBC (10^{12}/L)	0.190	< 0.001
Hemoglobin (g/L)	0.208	< 0.001
Triglyceride (mmol/L)	0.207	< 0.001
Cholesterol (mmol/L)	−0.006	0.867
HDL (mmol/L)	−0.091	0.032

HDL high density lipoprotein, *WBC* white blood cell, *RBC* red blood cell, *BMI* body mass index

Baseline PNI and new-onset pneumonia

Table 3 shows that patients with higher BMI, diabetes and older age were more likely to suffer from pneumonia after adjustment for covariates ($P<0.05$). After adjustment for age, BMI, complications, and laboratory measures, low PNI was an independent risk factor for pneumonia. Table 4 shows that the high PNI may reduce the risk of pneumonia in PD patients compared with the low PNI group (HR 0.479, 95% CI 0.297–0.772) by the adjusted Cox regression model.

Kaplan–Meier survival curves and log-rank tests showed a statistically significant difference in the first occurrence of pneumonia between the two groups (log-rank test, $P=0.016$) (Fig. 2). We also investigated the association between different subgroups (including men or women, whether diabetes mellitus, hypertension, over 60 years < 60 years) and the incidence of first pneumonia. The forest map in Fig. 3 showed that there is no interaction in those subgroups.

Discussion

This retrospective cohort study explored that the low PNI was a risk factor for pneumonia in patients with PD. To our knowledge, this is the first report on the effects of PNI on the occurrence of pneumonia in patients with PD.

Previous studies have shown that PNI was related to the occurrence of pneumonia in non-dialysis patients. A retrospective study showed that preoperative PNI was closely related to postoperative pneumonia in patients undergoing curative lung cancer resection [17]. Another study showed

Table 3 Significant risk factors for new-onset pneumonia

Variables	Univariate Cox analysis			Multivariate Cox analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (per 1-year greater)	1.029	1.016–1.042	< 0.001	1.027	1.001–1.052	0.004
BMI (per 1-kg/m^2 greater)	1.079	1.031–1.129	0.001	1.118	1.024–1.221	0.013
Smoking (yes vs. no)	1.837	1.185–2.848	0.007			
Drinking (yes vs. no)	2.066	1.052–4.058	0.035			
CVD (yes vs. no)	2.414	1.652–3.528	< 0.001			
Diabetes (yes vs. no)	2.334	1.680–3.472	< 0.001	1.801	1.025–3.166	0.041
Hypertension (yes vs. no)	2.265	1.506–3.407	< 0.001			
Hyperlipidemia (yes vs. no)	0.970	0.695–3.407	< 0.001			
Platelet (per 1–10^9/L greater)	1.004	1.001–1.006	0.004			
Creatinine (per1-umol/L greater)	0.999	0.999–1.000	0.001			
BUN (per 1-mmol/L greater)	0.964	0.944–0.983	< 0.001			
Hemoglobin (per 1-g/L greater)	1.010	1.001–1.019	0.036			
Cholesterol (per1-mmol/L greater)	1.223	1.075–1.391	0.002			
Triglyceride (per 1-mmol/L greater)	0.926	0.794–1.079	0.325			
HDL (per 1-mmol/L greater)	0.523	0.291–0.942	0.031			
Serum calcium (per 1-mmol/L greater)	4.860	2.667–8.853	< 0.001			
Phosphorus (per 1-mmol/L greater)	1.021	1.001–1.041	0.041			

BMI body mass index, *CVD* cardiovascular disease, *HDL* high-density lipoprotein, *BUN* Blood urea nitrogen, *HR* hazards ratio, *CI* confidence interval

Table 4 Univariate and multivariate adjusted hazard ratios for new-onset pneumonia PD patients

Risk factors	HR (95% CI)	*P*
Unadjusted	0.655 (0.462–0.929)	0.018
Model 1	0.692 (0.485–0.989)	0.043
Model 2	0.971 (0.946–0.997)	0.032
Model 3	0.479 (0.297–0.772)	0.003

Reference group is low PNI group

Model 1: BMI, age

Model 2: Model 1 plus smoking history, drinking history, and Comorbid conditions (Diabetes mellitus, Hypertension, Cardiovascular disease.)

Model 3: Model 2 plus platelet, total cholesterol, blood urea nitrogen, serum creatinine, high density lipoprotein, serum calcium, serum phosphorus, residual renal function

that PNI was independently correlated with the severity of coronavirus disease in 2019 [18]. No research has focused on the relationship between PNI and pneumonia in PD patients. The research on the relationship between prognosis and PNI in PD patients mainly focuses on all-cause mortality, cardiovascular events, and cardiovascular mortality [13, 19]. Yang reported that PNI had better predictive value in all-cause mortality and cardiovascular events in patients with PD [19].

Inflammation, immunity, and nutrition are closely related to each other in patients [20]. Long-term chronic inflammation can cause immune depression and malnutrition. At the same time, malnutrition can lead to immune deficit and acute infection. PEW is common in patients with chronic kidney disease, especially in patients undergoing peritoneal dialysis, and is associated with mortality and hospitalization rates for infections [21]. Inadequate food intake and changes caused by uremia, such as increased energy consumption, persistent inflammation, acidosis, and a variety of endocrine disorders are the main causes of PEW [22]. Many studies have shown that hypoalbuminemia was a strong indicator for PEW [23]. Serum albumin had a protective effect against endothelial dysfunction that related to inflammation and oxidative stress [24]. Serum albumin levels below 30 g/L are associated with a twofold increased risk of peritonitis [25]. However, serum albumin is unreliable in the diagnosis of PEW, because it is affected by many factors, such as inflammation, liver disease, diabetes. PNI is not only a nutritional index but also an immunological index. Low PNI means low albumin and/or decreased lymphocyte counts, which was closely associated with the occurrence of pneumonia in PD patients.

In this study, PNI was positively correlated with nutritional indicators, such as hemoglobin, triglyceride, and BMI. This proved that PNI can well reflect the nutritional status of patients. The results of our study showed that PNI was negatively correlated with HDL. Sangmee has shown that patients with low baseline HDL had a significantly increased risk of future pneumonia hospitalization over a median follow-up of more than 20 years [26], this result is in accordance with our results. Previous studies also showed old age, low BMI, and diabetes were all risk factors for pneumonia [4, 27]. Spearman correlation

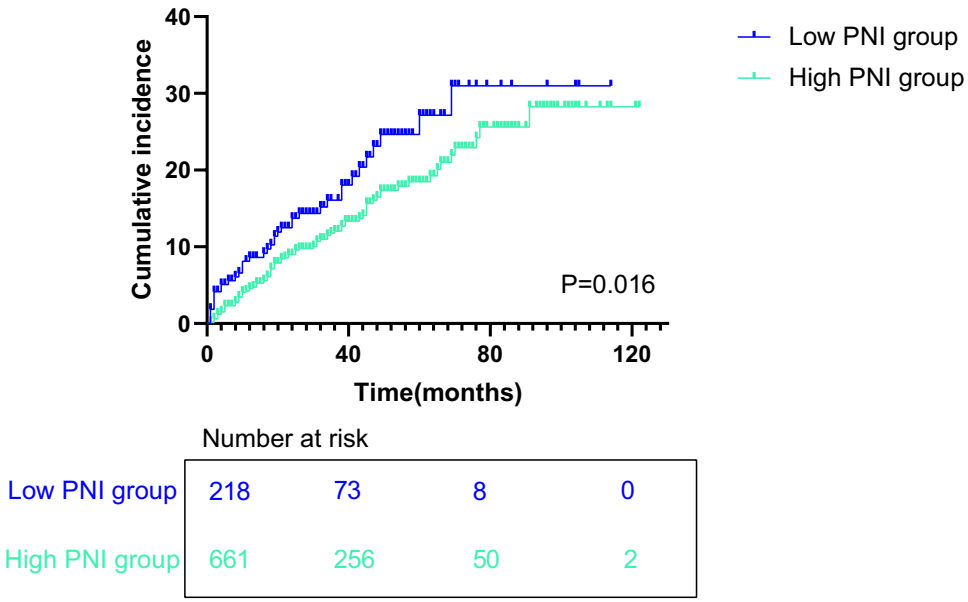

Fig. 2 Kaplan–Meier survival analysis was used to compare the incidence of new-onset pneumonia between the two groups

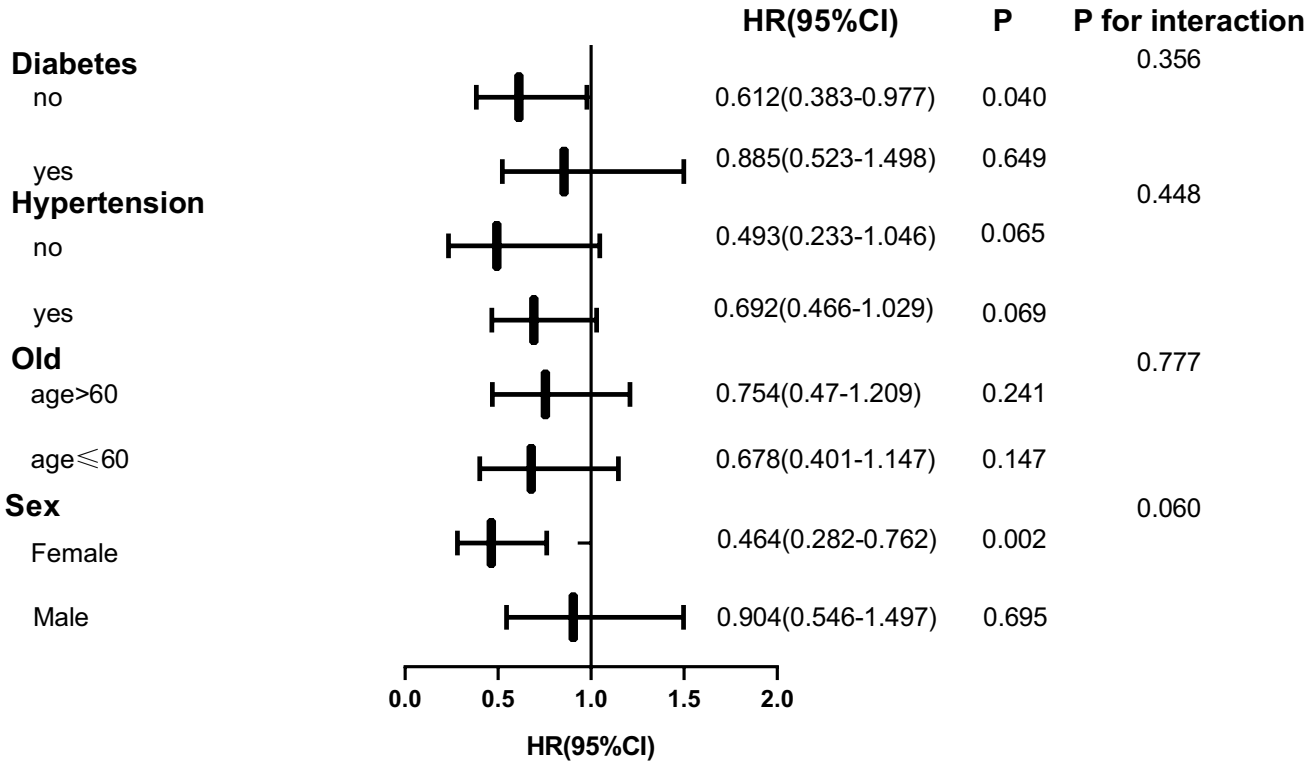

Fig. 3 Forest plot of relationship between PNI and new-onset pneumonia in different subgroups

analysis showed that PNI was negatively correlated with age in our study. The low levels of PNI represent the worse nutritional status of elderly patients. Although BMI is an immune and nutritional index, the standard of BMI is different in different races. This limits the use of BMI in comparing the nutritional and immune status of different races. While the correlation coefficient between PNI and anemia, protein metabolism and MBD was not high. The possible reasons are as follows: first, anemia is more related to erythropoietin and iron metabolism [28], but has a lower correlation coefficient with PNI which represents inflammation and nutrition. Second, the average PD

effluent protein loss was 6.41 ± 2.16 g/day [29]. The loss of protein will seriously affect the protein metabolism indicators, such as serum creatinine, BUN, and BMI, which is the reason why the correlation coefficient between PNI and the above-mentioned indexes is not high. Third, the MBD index is more affected by parathyroid function and dialysis adequacy [30], so the correlation coefficient with PNI is not high. Although the correlation coefficient is low, it may be suggestive that PNI may integrate and represent the prognostic value of all these factors.

In previous studies, the cutoff value of PNI ranged from 40 to 50 [31, 32]. At the moment, no large-scale study has given the exact cutoff value of PNI in predicting death, cardiovascular events, and inflammation. The cutoff value of PNI in our study is lower than that in other reports, possibly because the selected patients are different. The enrolled patients in our study were undergoing PD, and those patients are more likely to develop symptoms of protein malnutrition [33]. This study has some limitations that need to be addressed. First, although this was a multicenter retrospective study and important confounding factors were adjusted, there may still be some potential bias and limits the causality that can be inferred from observed associations. Second, baseline data were used in this study, but the follow-up laboratory data were lacking. Third, as the database has been established for a long time, we lack data on CRP and dietary. Fourth, the etiological data were not available for all patients with new-onset pneumonia, so the type of pneumonia in the patients could not be distinguished. Finally, our study did not determine the accurate cutoff value of PNI.

To prevent pneumonia in patients with peritoneal dialysis, the albumin and lymphocyte counts of patients should be monitored regularly, and the malnutrition and immune status of patients should be roughly assessed. Early and timely intervention can prevent the occurrence of pneumonia and reduce the incidence of complications caused by pneumonia.

Conclusions

PNI is a promising indicator for predicting inflammation. Low PNI is an independent risk factor for new-onset pneumonia in PD patients. Patients undergoing PD with the low level of PNI should improve nutritional status to avoid the occurrence of pneumonia.

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Declarations

Conflict of interest None of the patients had a potential conflict of interest.

Ethics approval and consent to participate The study proposal was conducted in accordance with the ethical principles of the Declaration of Helsinki and approved by the Institutional Review Board of the Sixth Hospital of Sun Yat-sen University (No. 2021SLYEC-177).

Consent for publication All authors are uniformly published.

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