Original Paper

High Neutrophil-to-Lymphocyte Ratio is a Significant Predictor of Cardiovascular and All-Cause Mortality in Patients Undergoing Peritoneal Dialysis

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Key Words

Peritoneal dialysis • Neutrophil-to-lymphocyte ratio • Arterial stiffness • Cardiovascular mortality

Abstract

Background/Aims: Chronic inflammation is associated with increased risk of cardiovascular death in patients with end-stage renal disease (ESRD). Although elevated neutrophil-to-lymphocyte ratio (NLR), a novel inflammatory marker, has been shown to predict cardiovascular disease and all-cause mortality in the general population, limited evidence is available for its role in ESRD. **Methods:** We enrolled 86 patients undergoing peritoneal dialysis (PD) for a 36-month follow-up to investigate the association between the NLR and arterial stiffness markers, namely, carotid-femoral pulse wave velocity (cfPWV) and carotid augmentation index (AIx), and mortality in PD patients. The primary endpoints were cardiovascular mortality and all-cause mortality. Kaplan–Meier curves were used to show the cumulative incidence of cardiovascular mortality and all-cause mortality. **Results:** High NLR was found to be a predictor of increased cfPWV ($\beta = 1.150$; $P < 0.001$) and AIx ($\beta = 3.945$; $P < 0.001$) in patients on PD. Patients with higher NLR had lower survival during follow-up. Kaplan–Meier curves showed that the cumulative incidences of both cardiovascular mortality and all-cause mortality were significantly higher in patients with $NLR \geq 4.5$ (both $P < 0.01$). **Conclusion:** Our results suggest that high NLR is independently associated with arterial stiffness and predicts cardiovascular and all-cause mortality in PD patients.

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Introduction

Cardiovascular disease is the main complication and major cause of death in patients undergoing peritoneal dialysis (PD), accounting for nearly 60% of all deaths in this population [1]. The high cardiovascular mortality associated with chronic renal disease, especially in patients with end-stage renal disease (ESRD), is not entirely explained by traditional cardiovascular risk factors [2]. Microinflammation is a key factor in the malnutrition-inflammation-atherosclerosis/calcification syndrome, which further accelerates the progression of atherosclerosis and is associated with increased risk of cardiovascular disease in patients on PD [3].

Neutrophil-to-lymphocyte ratio (NLR) is obtained simply by dividing the absolute neutrophil count by the absolute lymphocyte count in peripheral blood. Recently, NLR has been recognized as a novel inflammatory marker for assessing cardiovascular disease severity and poor prognosis in the general population [4] and in patients with ESRD [5, 6].

Increased arterial stiffness, an early marker of atherosclerosis, has been shown to be a powerful independent predictor of cardiovascular events and all-cause mortality in patients with chronic kidney disease (CKD) [7]. Carotid-femoral pulse wave velocity (cfPWV) and augmentation index (AIx) are widely used as surrogate markers of arterial stiffness [8]. An increasing number of studies have demonstrated that increased cfPWV is associated with increased risk of renal disease and incident cardiovascular events, as well as increased all-cause mortality [9-12].

However, to date there has been little evidence to show an association between NLR and arterial stiffness in patients on PD, and the prognostic value of NLR in this population is not yet entirely clear. Therefore, in this study, we evaluated the relationship between NLR and arterial stiffness markers, including cfPWV and AIx, and further investigated the association between increased NLR and mortality in patients on PD.

Materials and Methods

Data sources

One hundred five patients with ESRD receiving PD treatment in the Department of Blood Purification, Beijing Chao-Yang Hospital, Capital Medical University were recruited from January 2014 through December 2016. Inclusion criteria were ESRD with no residual renal function and regular PD treatment for at least 3 months. Exclusion criteria were clinical evidence of heart failure; a recent acute coronary or cerebrovascular event; autoimmune disease, malignancy or active infection; and medication history of aspirin, statins, steroids, or immunosuppressive drugs. Nineteen patients were excluded for the following reasons: clinical evidence of heart failure (n = 4), a recent acute coronary event (n = 3), a recent cerebrovascular event (n = 2), history of malignancy (n = 3), history of autoimmune disease (n = 3), clinical evidence of active infection (n = 2), and history of aspirin use (n = 2). The remaining 86 patients were undergoing continuous ambulatory PD treatment performed using Baxter Twin Bag (Baxter Healthcare, Guangzhou, China) with a daily dialysis dose of 6-8 L.

Patients were followed for 36 months. The primary endpoints were cardiovascular mortality and all-cause mortality. Cardiovascular death included death caused by coronary events, arrhythmias, sudden cardiac death, congestive heart failure, and cerebrovascular events [13]. The study was performed according to the Declaration of Helsinki and approved by the ethics committee of Beijing Chao-Yang Hospital, Capital Medical University. Written informed consent was obtained from each participant.

Biochemical measurements and calculation of NLR

Blood samples from study patients were taken after a 10-h overnight fast prior to dialysis. The blood samples were drawn into plastic vacutainers with EDTA (1 mg/mL of blood) for differential white blood cell

(WBC) count. NLR was calculated as the ratio of neutrophils to lymphocytes. Blood chemistry parameters were assayed by standardized and automated techniques in the same laboratory.

Arterial stiffness measurement

Common carotid artery stiffness was evaluated by cfPWV and AIx using the Complior SP System (Alam Medical, Vincennes, France) [14, 15], with participants in a supine position.

Carotid intima-media thickness measurement

Carotid intima-media thickness (IMT) was evaluated by carotid artery ultrasonography as described previously [16]. The presence of carotid plaque was defined as localized thickening (IMT $\geq$ 1.2 mm) that did not uniformly involve the whole wall of the carotid artery.

Statistical analysis

All data were analyzed using SPSS for Windows (Version 20.0, IBM Corp, Armonk, NY, USA). Continuous variables were presented as mean $\pm$ standard deviation ($\pm$ SD) or median (25th-75th percentile). Student's *t* tests, chi-square tests, or Mann-Whitney *U* tests were used to compare variables between groups, as appropriate. In addition, Spearman correlation was used for univariate analysis and logistic regression was used for multivariate analysis (confidence interval of 95%). Survival curves were estimated by Kaplan-Meier analysis and compared using the log-rank test. *P* values $<$ 0.05 were considered statistically significant.

Results

Patient characteristics

A total of 86 patients were enrolled in the study. Mean patient age was 54.6 ± 14.0 years (range 23-79 years) and the mean dialysis duration was 25.6 ± 11.2 months (range 7-51 months). The primary causes of ESRD were chronic glomerulonephritis (39.5%), diabetic nephropathy (17.4%), chronic interstitial nephritis (12.8%), hypertensive nephropathy (9.3%), and unknown causes (20.9%). Baseline patient characteristics are shown in Table 1.

Table 1. Baseline patient characteristics. Values are means $\pm$ SD or median (25th-75th percentile), unless specified otherwise. NLR = neutrophil-to-lymphocyte ratio; cfPWV = carotid-femoral pulse wave velocity; AIx = augmentation index; Hb = hemoglobin; Alb = albumin; ALT = alanine transaminase; AST = aspartate aminotransferase; TG = triglyceride; Tch = total cholesterol; LDL-C = low-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; Scr = serum creatinine; BUN = blood urea nitrogen; Ca = calcium; P = phosphorus; iPTH = intact parathyroid hormone; RASI = renin angiotensin system inhibitor; CCB = calcium channel blocker; β -blocker = β -receptor blocker

Items	Patients (n=86)
Age, years	54.6 $\pm$ 14.0
Sex, male, n (%)	37 (43.0%)
Primary disease	
Chronic glomerulonephritis, n (%)	34 (39.5%)
Diabetic nephropathy, n (%)	15 (17.4%)
Chronic interstitial nephritis, n (%)	11 (12.8%)
Hypertensive nephropathy, n (%)	8 (9.3%)
Unknown causes, n (%)	18 (20.9%)
PD duration, months	25.6 $\pm$ 11.2
Smoking, n (%)	9 (10.5%)
Diabetes, n (%)	16 (18.6%)
NLR	4.50 (2.50-5.97)
cfPWV, mm/s	10.1 $\pm$ 3.5
AIx, %	29.5 $\pm$ 17.6
Carotid plaque, n (%)	34 (49.3%)
Hb, g/L	114.6 $\pm$ 10.9
Alb, g/L	35.5 $\pm$ 3.3
ALT, U/L	17.4 $\pm$ 6.0
AST, U/L	19.2 $\pm$ 6.8
TG, mmol/L	1.74 $\pm$ 0.79
Tch, mmol/L	4.57 $\pm$ 0.76
LDL-C, mmol/L	2.91 $\pm$ 0.97
hsCRP, mmol/L	1.83 (1.49-4.11)
Scr, μ mol/L	888.4 $\pm$ 173.6
BUN, mmol/L	21.6 $\pm$ 6.3
Ca, mmol/L	2.20 $\pm$ 0.24
P, mmol/L	1.46 $\pm$ 0.32
iPTH, pg/ml	207.5 (147.3-250.0)
RASI, n (%)	44 (63.8%)
CCB, n (%)	54 (78.3%)
β -blocker, n (%)	24 (34.8%)

Table 2. Characteristics of PD patients with and without carotid plaque. Values are means $\pm$ SD or median (25th-75th percentile), unless specified otherwise. ^a $P < 0.01$, compared with non-plaque group. NLR = neutrophil-to-lymphocyte ratio; cfPWV = carotid-femoral pulse wave velocity; AIx = augmentation index; Hb = hemoglobin; Alb = albumin; ALT = alanine transaminase; AST = aspartate aminotransferase; TG = triglyceride; Tch = total cholesterol; LDL-C = low-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; Scr=serum creatinine; BUN = blood urea nitrogen; Ca = calcium; P = phosphorus; PTH = parathyroid hormone; RASI = renin angiotensin system inhibitor; CCB = calcium channel blocker; β -blocker = β -receptor blocker

Items	PD without carotid plaque group (n = 42)	PD with carotid plaque	P value
Age, years	55.7 $\pm$ 13.9	53.6 $\pm$ 14.2	0.499
Sex, male/female	18/24	19/25	0.976
PD duration, months	26.0 $\pm$ 10.8	25.3 $\pm$ 11.7	0.749
BMI, kg/m ²	24.0 $\pm$ 2.4	24.5 $\pm$ 3.0	0.409
Smoking, no.(%)	5(11.9)	4 (9.1)	0.670
Diabetes, no. (%)	7 (16.7)	9 (20.5)	0.652
NLR	2.96 (2.33-5.40)	5.07 (3.45-6.47) ^a	0.012
cfPWV, mm/s	8.9 $\pm$ 2.9	11.3 $\pm$ 3.7 ^a	0.001
AIx, %	24.2 $\pm$ 15.8	34.5 $\pm$ 17.9 ^a	0.006
Hb, g/L	114.7 $\pm$ 11.8	114.6 $\pm$ 10.4	0.921
Alb, g/L	35.6 $\pm$ 3.4	35.4 $\pm$ 3.2	0.729
ALT, U/L	17.4 $\pm$ 5.4	17.5 $\pm$ 6.6	0.928
AST, U/L	18.3 $\pm$ 5.7	20.1 $\pm$ 7.7	0.223
TG, mmol/L	1.78 $\pm$ 0.90	1.70 $\pm$ 0.68	0.643
Tch, mmol/L	4.52 $\pm$ 0.73	4.61 $\pm$ 0.80	0.574
LDL-C, mmol/L	2.92 $\pm$ 1.10	2.90 $\pm$ 0.84	0.946
hsCRP, mmol/L	1.74 (1.15-1.93)	3.99 (1.60-5.10) ^a	0.005
Scr, μ mol/L	853.9 $\pm$ 163.2	893.8 $\pm$ 153.2	0.222
BUN, mmol/L	21.7 $\pm$ 6.7	21.5 $\pm$ 5.9	0.855
Ca, mmol/L	2.20 $\pm$ 0.26	2.20 $\pm$ 0.22	0.986
P, mmol/L	1.50 $\pm$ 0.35	1.43 $\pm$ 0.28	0.325
PTH, pg/ml	204.0 (145.0-253.0)	228.5 (150.0-257.0)	0.447
RASI, no.(%)	26 (61.9)	31 (70.5)	0.402
CCB, no.(%)	32 (76.2)	36 (81.8)	0.521
β -blocker, no.(%)	14 (33.3)	11 (25.0)	0.395

Characteristics of PD patients with and without common carotid artery plaque

Forty-four of 86 patients (51.2%) had plaque in the common carotid artery as assessed by IMT. NLR was significantly higher in patients with carotid plaque than in patients without carotid plaque. Interestingly, cfPWV and AIx were also higher in patients with carotid plaque. However, there were no significant differences with respect to age, sex distribution, PD duration, body mass index, diabetes, smoking, hemoglobin, serum creatinine, blood urea nitrogen, triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C), or high-sensitivity C-reactive protein (hsCRP) between patients with and without carotid plaque (Table 2).

Correlation of NLR with arterial stiffness markers in PD patients

Correlations between NLR and patient characteristics are shown in Table 3. NLR was positively correlated with cfPWV ($r = 0.857$; $P < 0.001$), AIx ($r = 0.609$; $P < 0.001$), and hsCRP ($r = 0.515$; $P < 0.001$). NLR was not significantly correlated with age, sex, PD duration, smoking, diabetes, or serum LDL-C.

In the multivariate analysis, NLR was independently correlated with cfPWV ($\beta = 1.150$; $P < 0.001$) and AIx ($\beta = 3.945$; $P < 0.001$) (Table 4).

Table 3. Correlation analysis for variables and NLR in PD patients. cfPWV = carotid-femoral pulse wave velocity; AIx = augmentation index; LDL-C = low-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein

Variables	r	P value
Age, years	0.102	0.352
Sex	0.154	0.156
PD duration, months	0.088	0.420
Smoking	0.027	0.807
Diabetes	0.030	0.783
LDL-C, mmol/L	0.128	0.241
hsCRP, mmol/L	0.515	<0.001
cfPWV, mm/s	0.857	<0.001
AIx, %	0.609	<0.001

Table 4. Multivariate associations of cfPWV and A1x in PD patients. NLR = neutrophil-to-lymphocyte ratio; cfPWV = carotid-femoral pulse wave velocity; A1x = augmentation index; LDL-C = low-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein

Variables	cfPWV			A1x		
	β coefficient	t	P value	β coefficient	t	P value
Age	0.018	1.102	0.274	0.053	0.498	0.620
Sex	0.239	0.532	0.596	0.931	0.310	0.757
PD duration	0.012	0.617	0.539	0.089	0.664	0.509
Smoking	1.101	1.513	0.134	0.132	0.027	0.978
Diabetes	0.372	0.622	0.536	4.428	1.107	0.272
NLR	1.150	8.030	<0.001	3.945	4.126	<0.001
LDL-C	0.377	1.533	0.129	0.207	0.126	0.900
hsCRP	0.475	2.925	0.005	3.035	2.797	0.007

Fig. 1. Box plots for NLR levels in PD patients with all-cause and cardiovascular death. A. PD patients who died from all causes had significantly higher NLR levels ($P < 0.01$); B. PD patients who died from cardiovascular causes had significantly higher NLR levels ($P < 0.01$).

Fig. 2. Kaplan–Meier plots for all-cause mortality and cardiovascular mortality in PD patients. A. Patients with NLR ≥ 4.5 had significantly higher 36-month all-cause mortality (log rank = 25.162; $P < 0.01$); B. Patients with NLR ≥ 4.5 had significantly higher 36-month cardiovascular mortality (log rank = 25.530; $P < 0.01$).

NLR levels in PD patients with cardiovascular death and all-cause death

Of the 37/86 patients (43.0%) who died during the study period, 24 (64.9%) died of cardiovascular events. NLR was higher in patients who died of any cause vs those who survived (6.09 [4.99–7.56] vs 2.92 [2.30–4.65]; $P < 0.01$), as well as in patients who died of cardiovascular causes vs those who survived (6.57 [5.94–7.73] vs 2.98 [2.33–4.90]; $P < 0.01$) (Fig. 1 A and B).

Association of NLR with all-cause and cardiovascular death in PD patients

When patients were divided into 2 groups depending on median NLR (below or above the median value of 4.5), overall survival (log rank = 25.162; $P < 0.01$) and cardiovascular survival (log rank = 25.530; $P < 0.01$) were significantly lower in the group with higher NLR (Fig. 2 A and B).

Discussion

The results of this study demonstrate that elevated NLR is associated with arterial stiffness in patients undergoing PD. Multiple linear regression analysis showed that NLR is an independent factor for increased cfPWV and AIX. Interestingly, we further found that elevated NLR was a significant predictor of all-cause mortality and cardiovascular mortality in PD patients, independent of clinical, biochemical, and inflammatory parameters.

These findings are similar to those previously reported in the general population and in patients with ESRD, in which elevated NLR as a novel inflammation marker has been shown to be strongly and independently predictive of cardiovascular disease severity and mortality. In patients with severe calcific aortic stenosis, NLR was the independent prognostic factor most significantly associated with major adverse cardiovascular events [17]. In patients with pulmonary arterial hypertension, NLR was also useful for assessment of disease severity [18]. In patients with obstructive sleep apnea syndrome, NLR was independently associated with cardiovascular disease and was a predictor of disease severity [19]. Patients with type 2 diabetes who had high NLR would be more vulnerable to significant coronary artery disease and carotid artery atherosclerosis [20]. In medical inpatients with multiple chronic conditions, increased NLR was associated with mortality [21]. In patients with peripheral arterial occlusive disease, increased NLR was related with higher cardiovascular mortality [22]. Okay et al. [23] noted that laboratory measurement of NLR, which is relatively easy and inexpensive, might provide significant information regarding inflammation in CKD, including in predialysis and dialysis patients. Malhotra et al. [24] suggested that NLR could serve as a potential surrogate marker for CRP in hemodialysis patients. Similarly, Ahbap et al. [6] found that NLR was significantly positively correlated with hsCRP levels in patients with ESRD on maintenance hemodialysis. In patients on prevalent hemodialysis, NLR was also associated with all-cause mortality [25]. We recently reported that NLR was also associated with all-cause and cardiovascular mortality in patients on hemodialysis [26]. NLR was found to be an independent predictor of left atrium mechanical function and atrial electromechanical delay times in patients with ESRD receiving peritoneal dialysis or hemodialysis [27]. Turkmen et al. [5] also found that NLR could predict vascular calcification in patients with ESRD receiving peritoneal dialysis or hemodialysis. Recently, Cai et al. [1] reported that NLR was independently associated with brachial-ankle pulse wave velocity (baPWV) in patients on peritoneal dialysis. But to date, little was known of the prognostic value of NLR in patients undergoing PD. Although An et al. [28] reported in 2012 that NLR was a strong predictor for overall and cardiovascular mortality in peritoneal dialysis patients, they did not investigate the association between NLR and arterial stiffness. In the present study, we investigated the association between NLR and arterial stiffness markers, namely, cfPWV and AIX, and mortality in PD patients.

Cardiovascular disease is the leading cause of death in peritoneal dialysis patients [29]. Traditional risk factors such as hypertension, diabetes, hyperlipidemia, smoking, and male sex do not explain the abnormally high incidence of cardiovascular disease in this patient population. Inflammation, which is a central process in the development of cardiovascular disease, is prevalent in patients with CKD [30]. Patients affected by different stages of CKD, particularly those on hemodialysis, present with a marked activation of inflammatory processes, which exposes them to elevated risk of morbidity and mortality [31]. High levels of free radicals have been reported in the course of renal failure, while patients with advanced CKD accumulate low molecular weight toxins with pro-oxidant activity [32]. So far, many plasma inflammation markers of cardiovascular disease, such as CRP and interleukin-6, have been found to have great predictive value and applied to clinical practice [33]. However, measurement of these markers is relatively expensive and not easy to conduct on a widespread basis. NLR, which is obtained by dividing the absolute neutrophil count by the absolute lymphocyte count, is an emerging marker for assessing inflammation and has been found to be of great predictive value for cardiovascular disease.

Yombi et al. [34] found that NLR levels return to normal more quickly than CRP levels in a standard postoperative period after total knee arthroplasty. A recent study conducted by Yilmaz et al. indicated that NLR was better than CRP for predicting the occurrence of osteoporosis [35]. Several potential mechanisms may explain the association between NLR and cardiovascular disease: neutrophils are proinflammatory cells, which could aggravate endothelial dysfunction, activate macrophages, and promote foam cell formation [36]; meanwhile, lymphopenia is associated with the progression of atherosclerosis and adverse cardiovascular outcomes, which may be due to the apoptosis of lymphocytes [37]. NLR may therefore increase in several cardiovascular diseases, and it is more stable than individual WBC counts. Based on our research, NLR is a potentially effective and inexpensive predictor of cardiovascular and all-cause mortality in peritoneal dialysis patients. Arterial stiffness, a novel cardiovascular risk factor, has been shown as a strong and independent predictor of cardiovascular disease in patients with kidney disease [38]. cfpWV and AIx, markers of arterial stiffness, are considered independent predictors of major cardiovascular events [39]. To our knowledge, the present study is the first to examine the relationship of NLR with cfpWV and AIx. Although some studies have shown that cfpWV and baPWV exhibit similar associations with cardiovascular disease risk factors and clinical events in the general population [40], its applicability to patients on PD is still controversial. For example, one study showed that baPWV was not useful for risk stratification of systemic atherosclerotic morbidity and mortality in patients on hemodialysis [41]. Markers of arterial stiffness such as cfpWV and AIx are widely used to predict coronary artery disease and cardiovascular disease, especially in PD patients [42, 43]. NLR, which is obtained by dividing the absolute neutrophil count by the absolute lymphocyte count, is easily calculated from differential WBC counts, more stable for measurement than individual WBC counts, and less affected by conditions that could change individual cell counts. According to our findings, an easy and inexpensive laboratory measurement of NLR might provide significant information regarding arterial stiffness markers, including cfpWV and AIx, to help predict cardiovascular disease and all-cause mortality in patients undergoing PD.

However, there were some limitations to our study. First, this was a non-randomized, single-center study that included a relatively small number of patients, which may lead to selection bias. Second, we did not compare NLR with other inflammatory markers such as CRP, and therefore cannot assess their relative predictive value for cardiovascular disease.

Conclusion

This study demonstrated that increased NLR was independently associated with a higher risk of arterial stiffness and higher all-cause and cardiovascular death in peritoneal dialysis patients. NLR, which is easy to assess, may be a novel marker of cardiovascular disease in this patient population. Further research is required to elucidate the mechanism underlying the relationship between NLR and cardiovascular disease, and to identify effective anti-inflammatory treatments to prevent cardiovascular disease in peritoneal dialysis patients.

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Disclosure Statement

The authors declare no conflict of interest.

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