High Neutrophil/Lymphocyte Ratio as an Independent Risk Factor for the First Occurrence of Stroke in Peritoneal Dialysis Patients

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Keywords. neutrophil-to-lymphocyte ratio, peritoneal dialysis, stroke

Introduction. Though neutrophil/lymphocyte ratio (NLR) level appears to be related with stroke events in general population, its relationship with stroke in peritoneal dialysis (PD) patients is still uncertain. This study aims to investigate the association between NLR and the first occurrence of stroke in PD patients.
Methods. In this retrospective cohort study, 1507 PD patients were enrolled from four centers in China and stratified into tertiles of NLR levels. The incidence of the first occurrence of stroke was analyzed by Kaplan-Meier cumulative incidence curve among different NLR tertiles, competing risk analysis was used to calculate the incidence of the first occurrence of stroke in the presence of competing risk of other events, multivariable COX regression analysis was performed to estimate the hazard ratios (HRs) for the first occurrence of stroke, as well as forest plot was utilized to describe the relationship between NLR and the first occurrence of stroke in different subgroups.
Results. During follow-up, 84 new-onset stroke events were recorded. Kaplan-Meier cumulative incidence curves showed significant differences in the incidence of the first occurrence of stroke among three groups (log-rank test: $P < .001$). In competing risk analysis, the cumulative incidence curves for tertiles of NLR levels were highly significant for the first occurrence of stroke ($P < .001$), but they were not statistically different for the occurrence of other events. Compared to the lowest tertile of NLR level, the highest tertile was associated with increased risk of the first occurrence of stroke in the adjusted Cox model (HR = 2.39, 95% CI: 1.37 to 4.15; $P < .05$). As for forest plot, there was no interaction in all subgroups.
Conclusion. High NLR was an independent risk factor for the first occurrence of stroke in PD patients.

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INTRODUCTION

Stroke is the second leading cause of death worldwide and currently the leading cause of death in China, which contributes to a heavy disease burden.[1-4] It seems that people with chronic kidney diseases have the highest risk in suffering from subsequent cardiovascular disease (CVD).[5,6] Moreover, CVD become the main causes of mortality in end-stage renal disease (ESRD) patients maintaining dialysis.[7] Stroke is one of the major causes of cardiovascular mortality in the group.[8] What's more, patients relying on maintenance dialysis with ESRD have

remarkably greater stroke incidence and higher mortality of stroke than non-dialysis patients do.[9,10] Therefore, reliable prognostic factors, which could help to estimate patients at high risk of stroke for ESRD population, are needed.

Neutrophil to lymphocyte ratio (NLR) as a novel index could be used to predict stroke and stroke prognosis.[11] Fang YN *et al.* suggested NLR was one of the credible biomarkers, which had the advantage of predicting prognostic outcome among patients who had suffered acute ischemic stroke.[12] Tao C *et al.* also found that increased level of NLR was associated with poor 90-day outcome independently after intracerebral hemorrhage, while NLR may serve as a novel inflammatory biomarker after intracerebral hemorrhage.[13]

Since NLR has been associated with increased risk of stroke prognosis in non-dialysis patients, it may probably also predict the risk of stroke in PD patients. However, there is no published paper having indicated NLR level associates with the risk of stroke in PD patients. In this study, we aim to investigate the association of NLR and the first occurrence of stroke in PD patients.

MATERIALS AND METHODS

Participants

From January 1, 2010 to May 31, 2016, a total of 1652 patients were recruited from four PD centers. Of them, 145 were excluded for the following reasons: age younger than 18 years or older than 80 years (n = 34), PD was maintained for less than 3 months (n = 32), clinical evidence of active infection that happened in a month before returning to hospital (n = 37), history of hematological or autoimmune disease and taking glucocorticoid or immunosuppressive (n = 42). Above patients were excluded because those factors may influence NLR level. Finally, this study included 1507 patients. The Institutional Review Board of the four PD centers approved this retrospective study. Written informed consent was not required because we retrospectively collected available medical records in the hospital.

Baseline Investigations

Baseline demographic and clinical data were collected at the initiation of PD therapy. Biochemical parameters were collected 3 months after PD therapy was initiated. Patients who reported current use of insulin or oral hypoglycemic agents and/or who had a clinical diagnosis of type 1 or type 2 diabetes mellitus were considered to have diabetes mellitus.[14] Hypertension was recorded if the patient took antihypertensive drugs or had 2 separate blood pressure measurements ≥ 140/90 mmHg. CVD was defined as including coronary heart disease, myocardial infarction, angioplasty, coronary artery bypass or heart failure. Stroke was defined as including cerebral infarction, intracerebral hemorrhage and subarachnoid hemorrhage.

Laboratory measurements were obtained using standard methods in the clinical laboratory. Total Kt/V were calculated using PD Adequest software 2.0 (Baxter, Deerfield, IL). Medicine use was recorded based on prescriptions. The patients returned to these centers for quarterly evaluation, and trained nurses interviewed the patients by telephone monthly to assess general conditions.

Study Outcome

The outcome was the first occurrence of stroke since PD therapy. Stroke was defined as including cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage. Trained nurses asking about previous medical events during monthly phone interviews identified strokes, and then experienced doctors confirmed the diagnosis of stroke again or via review of medical records. All patients were followed until death, transfer to hemodialysis therapy, kidney transplantation, transfer of care from four centers or censoring on May 31, 2017.

Statistical Analysis

Participants were divided into tertiles of NLR levels (tertile 1 [lowest], < 2.74; tertile 2 [middle], 2.74 ≤ NLR < 4.00; and tertile 3 [highest], ≥ 4.00). Summary statistics by tertile of NLR level were presented. Based on the results of the normality test, all continuous variables are skewed distribution. The values for skewed variables were described as median (25^{th} to 75^{th} percentile) and categorical data were given as frequency and percentages. Differences among the tertiles of NLR level were tested using $\chi 2$ test for categorical variables, Mann-Whitney U test for skewed continuous variables. A univariable logistic regression model was used to examine the association between patients' characteristics and new-onset stroke events since PD therapy with lower category as reference,

and then a multivariable logistic regression was used to examine patients' characteristics with predictive odds of the first occurrence of stroke, which adjusted for covariates with ($P < .05$ in univariable logistic analysis). Kaplan-Meier cumulative incidence curves were used to analyze the incidence of the first occurrence of stroke, and differences among distributions of incidence of new-onset stroke events were assessed by log-rank test. Competing risk analysis was used on the first occurrence of stroke and other events, and differences were assessed by Gray's test. Cox regression models were used to evaluate the relationship among the tertiles of NLR level with the first occurrence of stroke in PD patients, initially without adjustment and subsequently adjusting for several groups of covariates. The multivariable Cox regression model was constructed using eligible covariates that demonstrated significant or near-significant association with the first occurrence of stroke ($P < .05$) on multivariable analysis or characteristics ($P < 0.01$) list in Table 1 or for

Table 1. Demographic and Baseline Clinical Data for the Study Patients

Variables	Total (n = 1507)	Tertile 1 (n = 502)	Tertile 2 (n = 509)	Tertile 3 (n = 496)	*P*
No. of C1/C2/C3/C4	316/794/36/361	124/249/9/120	130/249/7/123	62/296/20/118	< .001
No. of Men/Women	855/652	262/240	275/234	318/178	< .001
NLR	3.4 (2.5, 4.5)	2.2 (1.8, 2.5)	3.4 (3.0, 3.8)	5.4 (4.6,7.0)	< .001
Demographics					
Age, y	51 (41, 62)	49 (39, 61)	50 (41, 61)	53 (43,63)	< .001
BMI, kg/m^2	22.1 (20.0, 24.3)	22.0 (20.0, 24.2)	22.0 (20.1, 24.4)	22.1 (20.0,24.3)	> .05
Comorbid					
Systolic BP, mmHg	149 (132, 164)	146 (130, 160)	149 (134, 161)	150 (134,170)	> .05
Diastolic BP, mmHg	87 (78, 95)	87 (78, 95)	87 (80,95)	87 (78,96)	< .001
Hypertension, n (%)	990 (65.7)	312 (62.2)	321 (63.1)	357 (72.0)	< .05
Diabetes Mellitus, n (%)	346 (23.0)	106 (21.1)	116 (22.8)	124 (25.0)	> .05
Cardiovascular Disease, n (%)	136 (9.0)	47 (9.4)	44 (8.6)	45 (9.1)	> .05
Stroke Disease, n (%)	80 (5.3)	22 (4.4)	26 (5.1)	32 (6.5)	> .05
Laboratory Variables					
Hemoglobin, g/L	87 (74, 100)	89 (76, 103)	88 (76, 101)	82 (70,95)	< .05
Albumin, g/L	34.5 (31.1, 37.9)	34.9 (31.3, 38.4)	34.7 (31.3, 37.5)	34.2 (30.5,37.3)	< .001
Creatinine, μmol/L	710.0 (544.0, 933.4)	699.5 (543.8, 899.5)	711.0 (541.9, 931.1)	729.5 (546.0,950.0)	< .001
Urea nitrogen, mmol/L	20.47 (15.50, 26.85)	19.4 (15.1, 25.4)	20.2 (15.3, 26.4)	22.0 (16.4,29.3)	< .001
Uric acid, mmol/L	428 (355, 509)	430 (356, 512)	427 (354, 504)	426 (358,502)	< .05
FBG, mmol/L	4.7 (4.1, 5.5)	4.6 (4.1, 5.4)	4.7 (4.1, 5.5)	4.8 (4.1,5.7)	< .001
Total Cholesterol, mmol/L	4.2 (3.5, 5.0)	4.3 (3.6, 5.1)	4.2 (3.5, 5.0)	4.1 (3.4,4.9)	> .05
Total Triglycerides, mmol/L	1.3 (1.0, 1.8)	1.4 (1.0, 1.9)	1.4 (1.0, 1.9)	1.3 (0.9,1.7)	> .05
Sodium, mmol/L	140.0 (138.0, 142.3)	140.7 (138.1, 142.5)	140.0 (138.0, 142.9)	140.0 (137.6,142.0)	> .05
Chlorine, mmol/L	103.0 (99.3, 107.0)	103.2 (100.0, 107.0)	103.0 (99.3, 106.8)	102.8 (99.0,107.0)	> .05
Calcium, mmol/L	2.0 (1.9, 2.2)	2.1 (1.9, 2.2)	2.1 (1.9, 2.2)	2.0 (1.8,2.1)	> .05
Potassium, mmol/L	4.1 (3.6, 4.7)	4.2 (3.7, 4.8)	4.1 (3.6, 4.7)	4.1 (3.6,4.8)	< .05
Phosphorus, mmol/L	1.7 (1.4, 2.0)	1.6 (1.4, 2.0)	1.6 (1.3, 2.0)	1.8 (1.4,2.1)	< .001
Alkaline Phosphatase, U/L	73 (58, 94)	71 (56, 91)	73 (59, 91)	76 (60,99)	< .001
Total Kt/V	2.3 (1.8, 2.6)	2.3 (1.8, 2.7)	2.4 (1.7, 2.6)	2.2 (1.8,2.6)	> .05
RRF, mL/min	4.6 (2.1, 15.0)	4.4 (2.0, 13.4)	4.6 (2.2, 15.1)	4.7 (2.0,16.5)	> .05
Treatments					
CCB, n (%)	1108 (73.5)	371 (73.9)	371 (72.9)	366 (73.8)	> .05
ACEI/ARB, n (%)	554 (36.8)	186 (37.1)	199 (39.1)	169 (34.1)	> .05
Loop Diuretic, n (%)	101 (6.7)	33 (6.6)	30 (5.9)	38 (7.7)	> .05
Insulin, n (%)	232 (15.4)	75 (14.9)	71 (13.9)	86 (17.3)	> .05
Aspirin, n (%)	135 (9.0)	42 (8.4)	44 (8.6)	49 (9.9)	> .05
Time, mo	30.6 (18.9, 46.9)	33.0 (20.1, 50.8)	32.6 (21.4, 47.3)	27.9 (16.3,41.5)	< .001

Note: All continuous variables are skewed distribution, the values for continuous variables are given as median (P25, P75). Time refer to time from the onset of peritoneal dialysis to the first occurrence of stroke events.
Abbreviations: C1,center 1; C2,center 2; C3,center 3; C4,center 4; NLR, neutrophil lymphocyte ratio; BMI, body mass index; FBG, fasting blood-glucose; Kt/V, K (dialyzer clearance of urea), t (dialysis time), V (volume of distribution of urea); RRF, residual renal function; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker.

importance of clinical concern. Moreover, the interaction between subgroups variable of interest including sex, age, history of diabetes mellitus and NLR group were examined by performing a formal test of interaction. Forest plot was used to represent the relationship between NLR and new-onset stroke events in each subgroup. In Cox regression models, time at risk was from study entry until death, transferring to hemodialysis therapy, kidney transplantation, transferring care from our center, or the end of study on May 31, 2017. For primary effects, $P < .05$ was considered statistically significant. Statistical analyses were performed using SPSS version 23 and R software (version R-3.6.1, www.r-project.org).

RESULTS

Participants

Baseline demographic and clinical characteristics of the cohort were given in Table 1, divided according to tertiles of NLR levels. A total of 1507 patients were enrolled in this study (median age, 51 (41, 62) years; 56.7% men; 23.0% with diabetes; 65.7% with hypertension), with a median follow-up of 30.6 (maximum, 89.4) months. Median NLR value was 3.4 (2.5, 4.5) for all patients. In the whole process, 78 (5.2%) patients underwent kidney transplantation after a median of 20 months, 199 (13.2%) were transferred to hemodialysis therapy for any reason after a median of 28 months, 20 (1.3%) transferred to other center after a median of 36 months, and 25 (1.7%) lost to follow up. Stroke events were registered during follow-up. A total of 84 stroke events (5.6%) were recorded. (Figure 1).

NLR Associated with the First Occurrence of Stroke in PD Patients

The significant risk factors for new-onset stroke events were given in Table 2 by adjusting for covariates ($P < .05$ univariable logistic regression). The first occurrence of stroke was associated with male, history of hypertension, stroke and CVD as well as higher FBG. Associations of NLR with new-onset stroke events with defined models (with the group 1 as the reference group) are listed in Table 3. Regardless of the adjustment method used, the highest tertile of NLR level was associated significantly with the first occurrence of stroke compared to the lowest tertile.

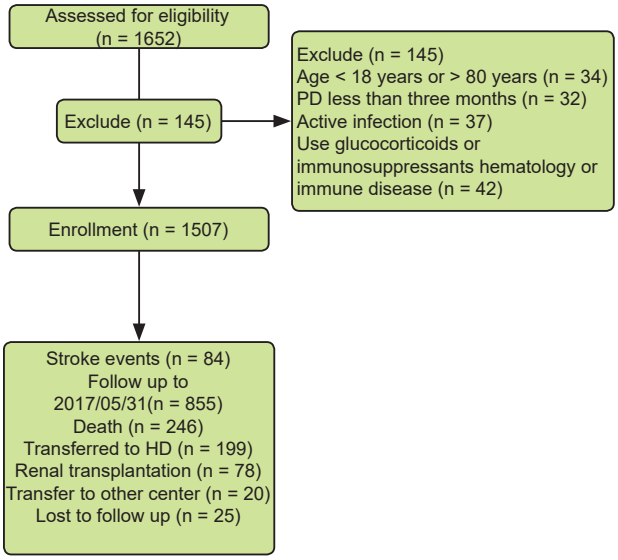

Figure 1. It shows study algorithm, including patient enrollment and outcomes. (PD, peritoneal dialysis; HD, hemodialysis).

Table 2. Significant Risk Factors for the First Occurrence of Stroke

Risk Factors	OR (95% CI)	*P*
Univariable Logistic Regression		
Sex (Female vs. Male)	0.45 (0.27 to 0.74)	< .05
Diabetes Mellitus (Yes vs. No)	2.17 (1.38 to 3.44)	< .05
Hypertension (Yes vs. No)	2.51 (1.42 to 4.43)	< .05
History of Stroke Disease (Yes vs. No)	3.32 (1.72 to 6.41)	< .001
Cardiovascular Disease (Yes vs. No)	2.78 (1.58 to 4.89)	< .001
FBG (> 1-mmol/L)	1.12 (1.05 to 1.20)	< .05
Use of ACEI/ARB (Yes vs. No)	1.69 (1.09 to 2.63)	< .05
Use of Insulin (Yes vs. No)	1.92 (1.14 to 3.21)	< .05
Multivariable Logistic Regression		
Sex (Female vs. Male)	0.43 (0.26 to 0.71)	< .05
Hypertension (Yes vs. No)	1.98 (1.10 to 3.56)	< .05
History of Stroke Disease (Yes vs. No)	2.53 (1.29 to 4.99)	< .05
Cardiovascular Disease (Yes vs. No)	1.95 (1.05 to 3.64)	< .05
FBG (> 1-mmol/L)	1.09 (1.01 to 1.17)	< .05

Note: Multivariable logistic regression adjusted for covariates ($P < .05$) list in univariable logistic regression. Abbreviations: OR, odds ratio; CI, confidence interval; FBG, fasting blood-glucose; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker.

In crude analysis, the Kaplan-Meier cumulative incidence curves showed there were significant differences in the incidence of new-onset stroke events among the tertiles of NLR level (log-rank test: $P < .001$, Figure 2). In competing risk analysis, cumulative incidence curves for each tertile of NLR level are highly significant for the first occurrence

Table 3. Relationship Between Tertiles of NLR and the First Occurrence of Stroke

	Tertile 2 (n = 509)		Tertile 3 (n = 496)	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Unadjusted	1.09 (0.57 to 2.07)	> .05	3.15 (1.83 to 5.43)	< .001
Model 1	1.03 (0.54 to 1.97)	> .05	2.58 (1.49 to 4.46)	< .05
Model 2	1.00 (0.53 to 1.91)	> .05	2.55 (1.47 to 4.41)	< .05
Model 3	0.99 (0.52 to 1.88)	> .05	2.39 (1.37 to 4.15)	< .05

Note: Reference group is Tertile 1.
Model 1: sex, age, BMI
Model 2: Model 1 plus comorbid conditions (diabetes mellitus, hypertension, stroke disease, cardiovascular disease) and medical history (aspirin)
Model 3: Model 2 plus albumin, creatinine, urea nitrogen, uric acid, FBG, total cholesterol, total triglycerides, phosphorus, alkaline phosphatase
Abbreviations: NLR, neutrophil lymphocyte ratio; BMI, body mass index; FBG, fasting blood glucose; HR, hazard ratio; CI, confidence interval.

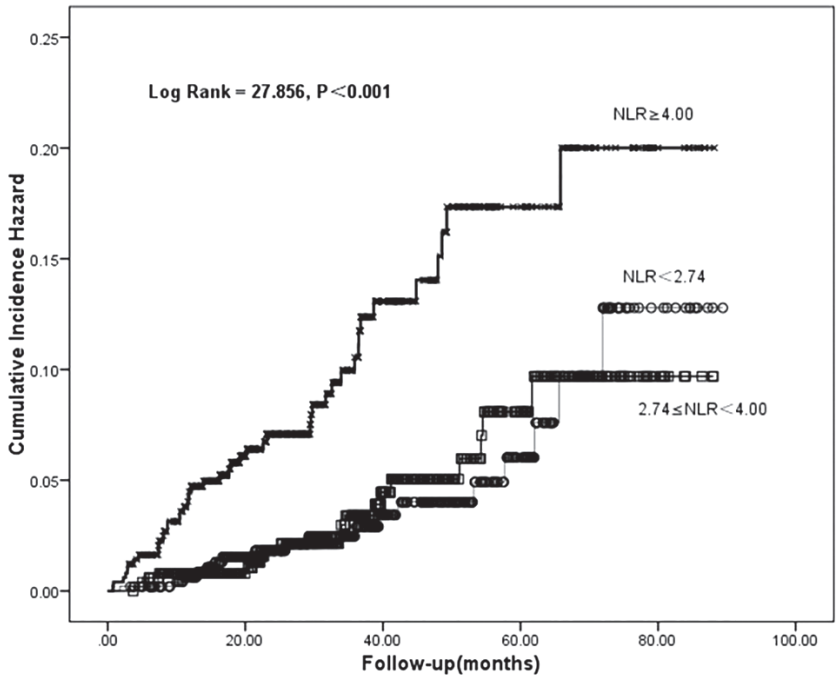

Figure 2. It demonstrates cumulative incidence of the first occurrence of stroke in 1507 peritoneal dialysis patients by NLR. The curves were constructed using the Kaplan–Meier method and compared using the Mantel–Cox log-rank test. Patients in the highest tertile of NLR level showed higher incidence of the first occurrence of stroke.

of stroke ($P < .001$), but they are not statistically different for transfer to hemodialysis therapy ($P > .05$), kidney transplantation ($P > .05$), transfer to other center ($P > .05$), being lost to follow up ($P > .05$), and death ($P > .05$) (Figure 3).

NLR Associated with the First Occurrence of Stroke in Different Subgroups

We investigated the association between NLR and the first occurrence of stroke in different subgroups which we were interested in, including male or female, with or without diabetes, old age (≥ 60 years) or young age (< 60 years). These subgroups were analyzed by COX regression and represented as a forest plot. No interaction was found in all subgroups (Figure 4).

DISCUSSION

This retrospective cohort study indicated that the incidence of first occurrence of stroke was significantly higher in Tertile 3, while compared to Tertile 1. It indicated that elevated NLR was associated with new-onset stroke events risk in PD patients, after adjusting possibly related confounders.

As is well-known, the relationship between chronic inflammation and CVD has been studied widely.[15] Elevated WBC was reported to be related to CVD,[16] in which neutrophils played a significant predictive role.[17] NLR, as a simple ratio readily obtained from inexpensive blood routine examination, has been reported that its predictive value was higher than individual cell counts.[15]

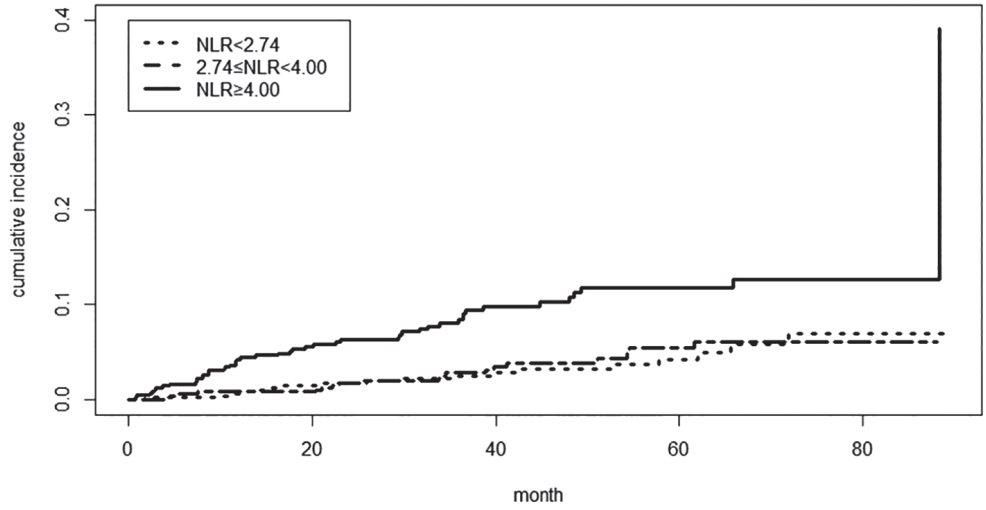

Figure 3. It shows estimated cumulative incidence curves with the first occurrence of stroke. The cumulative incidence curves for the tertiles of NLR level were highly significant for the first occurrence of stroke ($P < .001$), but they were not statistically different for transfer to hemodialysis therapy, kidney transplantation, transfer to other center, lost to follow up and death as competing events for each type of NLR level.

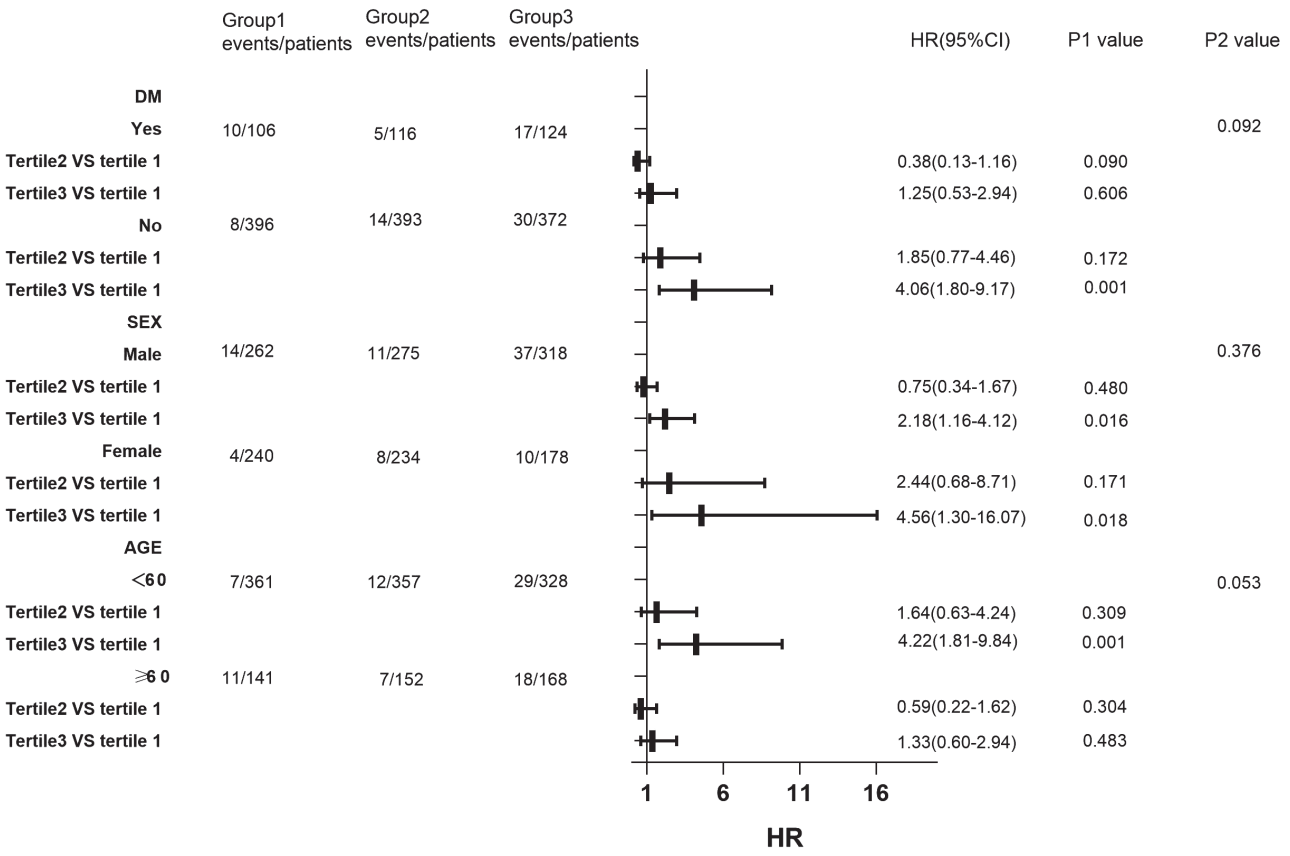

Figure 4. It demonstrates forest plot of relationship between NLR and the first occurrence of stroke in different subgroups.
Note: The *P*1 value corresponded to the relationship between NLR and the first occurrence of stroke in different subgroups. The *P*2 value corresponded to the interaction test between the NLR and the subgroups variable of interest. No interaction was observed for age, diabetes mellitus and sex in the first occurrence of stroke. Adjusted model: sex, age, BMI, history of diabetes mellitus, hypertension, stroke and cardiovascular disease, use of aspirin, albumin, creatinine, urea nitrogen, uric acid, FBG, total cholesterol, total triglycerides, Phosphorus, alkaline phosphatase (in particular, the adjustment model should exclude its own factors in different subgroups. For example, in the age subgroup, the adjustment model did not include age.) Abbreviations: NLR, Neutrophil / Lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

Plenty of studies have indicated that the occurrence, development and mortality of coronary heart disease could be predicted by increased NLR level independently.[16,18-21] It has also been proved that NLR showed perfect predictive value in stroke,[11] which was relevant to the prognosis of cerebral hemorrhage and infarction.[13,22] A large-scale retrospective cohort study enrolled 24708 generally healthy screened people, it was demonstrated that subjects with increased NLR tended to have elevated risk for the incidence of ischemic stroke.[23] Luo P *et al.* reported that elevated NLR was positively related with cerebral hemorrhage incidence in T2DM patients.[24] These two studies have confirmed that NLR was associated with the incidence of stroke in non-dialysis population. However, few study investigated the relationship between NLR and the occurrence of stroke in dialysis patients.

So far, only one study[25] explored the relationship of NLR level and the occurrence of cardiovascular events in incident dialysis patients. The prospective cohort study, which, enrolled 86 PD patients with median of NLR equal to 3.72 showed that elevated NLR was associated with increased risk of CVD events (3.02, 95% CI: 1.32 to 8.00; $P < .05$). However, the association between NLR and stroke events has not been investigated independently. And some problems in the study should be pointed out: Firstly, the number of patients they enrolled was small; Secondly, they did not exclude patients who suffered from those diseases which altered NLR; Thirdly, they included patients receiving different dialysis treatment, which might be influential in CVD events. Yet the potential role of NLR as a simple and easily obtained indicator needs to be confirmed by multicenter prospective studies with relatively scientific grouping methods in the future.

In our study, a total of 1507 PD patients were included and stratified into tertiles of NLR levels. Multivariable Cox regression analysis showed that NLR was significantly associated with the first occurrence of stroke. This conclusion was consistent with the previous study.[23] Moreover, we investigated whether NLR independently predicted the new-onset stroke events in different subgroups. However, the result was negative.

Some strength could be found in our study. First, the number of patients we enrolled from multicenter was relatively large. Second, the association between NLR levels and the first occurrence of stroke were investigated independently for the first time in PD patients, instead of exploring the relationship between NLR and CVD events. Third, we finished a detailed evaluation and adjustment for stroke risk factors.

There were several limitations in this study. Firstly, because the patients were from four centers, some data was lack and not considered, such as CRP, smoking history and other confounding factors, which may influence the NLR value and statistical results. We should try to fill up previous flaw data through available information of patients and pay more attention to collecting new data carefully in the future. Secondly, our study was a retrospective cohort study rather than a prospective study. So, it is necessary to initiate a prospective study about the relationship between NLR and the new-onset stroke events in PD patients. Thirdly, all the parameters were measured on a single occasion at baseline and did not take into account changes over time. Some dynamic data of those patients should be included to strength the conclusion. Fourthly, in this study, we cannot analyze the association of NLR and the first occurrence of every type of stroke respectively, for not paying attention to registering the types of stroke when collecting data. In that case, the pathogenic hypothesis about NLR and the first occurrence of stroke in PD patients was not stated in this study.

CONCLUSION

In conclusion, our study demonstrated that high NLR is an independent risk factor for the first occurrence of stroke in PD patients. Although further study is needed, NLR could be considered as a useful and inexpensive marker for identifying higher risk for stroke in PD patients.

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DISCLOSURE

The authors declare that they have no financial conflicts of interest.

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