Platelet-to-Lymphocyte Ratio is Associated with the Mortality in Peritoneal Dialysis Patients

Siyi Liu, Mei Yang, Qing Zhao, Li Zhang, Qinkai Chen, Yu Wang

Department of Nephrology, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi 330006, China

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Original Paper

Introduction. Platelet-to-lymphocyte ratio (PLR) is widely used as an inflammatory marker and is associated with poor prognosis in some diseases, such as cardiovascular diseases and malignancies. However, the association between the PLR and all-cause mortality in peritoneal dialysis (PD) patients is unclear.

Methods. A total of 939 patients were enrolled. The X-tile program was performed to calculate the optimal cut-off values for the PLR, and the patients were divided into three groups according to the cut-off values: a low PLR group (< 108.33), medium PLR group (108.33 to 257.50), and high PLR group (> 257.50). Multivariate analysis was performed to assess the prognostic value of PLR. The primary end point was all-cause mortality.

Results. Of the 939 patients, the mean age was 49.9 years, and 57% of the patients were male. During a median follow-up of 27.5 months (interquartile range, 13.6-41.6 months), 221 (23.5%) died, in whom 114 (51.6%) deaths were attributed to cardiovascular mortality. Patients in the high PLR group had a higher mortality rate than patients in the low PLR group (log rank = 13.75, $P < .001$). The 1-year and 3-year overall survival rates were 88.9% and 71.7% for patients in the high PLR group compared with 98.6% and 86.2% for patients in the low PLR group, respectively. Similarly, multivariate Cox regression analysis showed that the mortality rate was higher in the high PLR group than in the low PLR group (HR = 1.64, 95% CI: 1.02 to 2.63, $P < .05$).

Conclusion. An increased PLR value was independently associated with all-cause mortality in PD patients.

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INTRODUCTION

Peritoneal dialysis (PD) is one of the major treatments for end-stage renal disease (ESRD) patients.[1] Compared with the general population, ESRD patients have a higher risk of mortality.[2] Cardiovascular disease (CVD) is the major cause of death in PD patients, accounting for nearly 60% of all deaths in PD patients.[3] Chronic inflammation, a key factor in the pathogenesis of atherosclerosis, plays a vital role in the pathogenesis of CVD in patients with ESRD.[4-6] Among various inflammatory markers, white blood cell subtypes have been considered to play a vital role in the pathogenesis of atherogenesis and atherothrombosis, which are closely related to cardiovascular adverse events.[7,8] Moreover, as an easy-to-measure indicator, the relationship between the ratio of blood cells and the prognosis of many diseases has been a hot topic. For example, recently, neutrophil to lymphocyte ratio (NLR) is reported associated with the first occurrence of stroke in PD patients.[9] Moreover, the platelet-to-lymphocyte ratio (PLR), is another one of the ratio of blood cells, which is simply obtained by dividing the absolute platelet count by the absolute lymphocyte count in

peripheral blood, is an inexpensive (low-cost), easily accessible novel inflammatory marker and has been a "hot topic" as a useful marker of CVD as well as an independent predictor of mortality risk.[10-13] Recently, many studies have shown that the PLR is associated with poor prognosis in various diseases, including CVD,[10] tumors,[14,15] chronic obstructive pulmonary disease,[16] liver cirrhosis,[17] and chronic kidney disease.[18] Furthermore, many studies have shown that the PLR may predict mortality among hemodialysis (HD) patients.[19,20] However, to date, data on the relationship between the PLR and mortality are limited among PD patients.

Therefore, in this study, we aimed to investigate the relationship between the PLR and all-cause mortality in PD patients, and we tested the hypothesis that a higher PLR level was associated with a higher all-cause mortality risk.

MATERIALS AND METHODS

We retrospectively extracted, refined, and examined data from all ESRD patients aged ≥ 18 years who underwent PD from November 1, 2005, to February 28, 2017, and who underwent PD treatment for at least 3 months in the PD center of The First Affiliated Hospital, Nanchang University, Jiangxi, China. The main exclusion criteria were as follows: 1) patients catheterized in other hospitals or transferred from permanent HD or patients who experienced failed renal transplantation; and 2) the presence of acute infection, malignancy, or hematological disease, as they could affect the lymphocyte and platelet counts; in addition, malignancy could adversely affect survival. The flow diagram is shown in Figure 1. Patients were followed from the first date of dialysis until death, kidney transplantation, being lost to follow-up, or the date of final follow-up assessment in all patients (May 31, 2017). Written informed consent was obtained from all patients. All study procedures complied with the ethical guidelines of the Declaration of Helsinki and were approved by the Human Ethics Committees of Nanchang University. The primary end point was defined as all-cause mortality. All baseline data were collected within a 3-month period, starting from the date of first PD therapy. Baseline demographic data included age, sex, primary cause of ESRD, presence of diabetes and CVD and smoking habits. Clinical and biochemical data included body mass index (BMI), blood pressure, estimated glomerular filtration rate (eGFR), hemoglobin, white blood cells, platelets, lymphocytes, serum albumin, serum uric acid, total cholesterol (CHOL), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and apolipoprotein-A1 (Apo-A1). Baseline residual renal function was assessed by eGFR using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[21] The PLR ratio was obtained by dividing the platelet count by the absolute lymphocyte count.

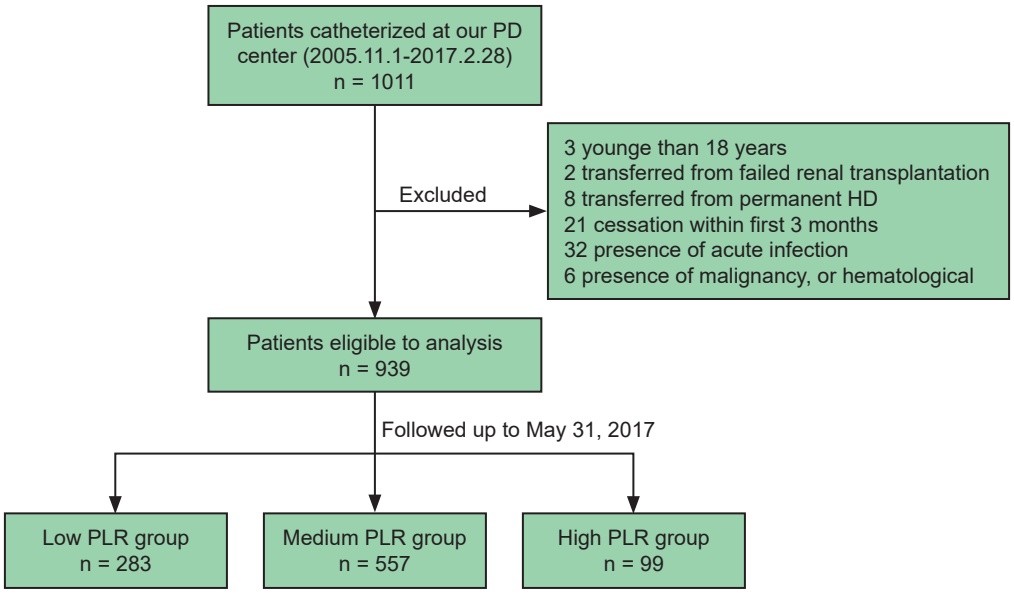

Figure 1. Flow Chart of This Study (Abbreviations: PD, peritoneal dialysis; HD, hemodialysis; PLR, platelet-to-lymphocyte ratio)

Statistical Analysis

We used the X-tile program, which is a new bioinformatics tool for biomarker assessment and outcome-based cut-off point optimization,[22] to select the optimal cut-off value for the PLR. According to the X-tile program, the optimal cut-off values for the PLR were 108.33 and 257.50. Then, we divided the patients into three groups according to the cut-off values: low PLR group (< 108.33), medium PLR group (108.33 to 257.50), and high PLR group (> 257.50). Continuous data were represented by the mean ± standard deviation (SD) or median (interquartile range, IQR); categorical data were represented by frequencies and percentages. The Chi-square test was used for the comparison of categorical variables. One-way ANOVA or Kruskal-Wallis tests were used to test for differences in continuous factors among the three groups. Survival curves were constructed based on cumulative incidences with Kaplan-Meier estimates and were compared using the log rank test. The associations between the PLR value and all-cause mortality were examined in Cox proportional hazards models. The censored data included switching to HD, renal transplantation, moving to another center, declining additional treatment, lost to follow-up, or still at our PD center on May 31, 2017. Multivariate Cox proportional hazards regression analyses were adjusted for variables with a significance level of $P < .10$ in univariate analysis or thought to be clinically significant. Kaplan-Meier plots were performed using R version 3.6.0 (http://www.r-project.org), and the other descriptive and multivariate analyses were conducted using SPSS version 21.0 (SPSS, Inc., Chicago, IL). A value of $P < .05$ was considered statistically significant.

RESULTS

Baseline Patient Characteristics

A total of 939 patients were included in the study, of whom the mean ± SD age was 49.9 ± 14.6 years, and 535 patients were male (57%). Table 1 lists the baseline clinical and biochemical characteristics of each of the three groups based on their PLR values

Table 1. Baseline Characteristics of Individuals Stratified by PLR.

Variables	Total	PLR			*P*
		Low < 108.33 (n = 283)	108.33 ≤ Medium ≤ 257.50 (n = 557)	High > 257.50 (n = 99)	
Age, y	49.9 ± 14.6	47.9 ± 15.0	50.2 ± 14.0	54.2 ± 15.6	< .05
Male, n (%)	535 (57.0)	144 (50.9)	341 (61.2)	50 (50.5)	< .05
PD duration, mo	27.5 (13.6, 41.6)	30.4 (16.6, 46.6)	26.9 (12.7, 40.8)	23.3 (11.3, 38.6)	< .05
BMI, kg/m^2	21.90 ± 3.35	21.68 ± 3.52	22.03 ± 3.19	21.82 ± 3.71	> .05
Smoking Status, n (%)	161 (17.1)	38 (13.4)	107 (19.2)	16 (16.2)	> .05
Etiology of ESRD					
Chronic Glomerulonephritis, n (%)	605 (64.4)	200 (70.7)	354 (63.6)	51 (51.5)	< .05
Diabetes Kidney Disease, n (%)	156 (16.6)	32 (11.3)	103 (18.5)	21 (21.2)	
Hypertension Nephropathy, n (%)	118 (12.6)	38 (13.4)	61 (11.0)	19 (19.2)	
Others, n (%)	60 (6.4)	13 (4.6)	39 (6.9)	8 (8.1)	
CVD, n (%)	95 (10.1)	23 (8.1)	60 (10.8)	12 (12.1)	> .05
Systolic Pressure, mmHg	146.78 ± 25.78	145.24 ± 25.96	147.38 ± 25.74	147.81 ± 25.55	> .05
eGFR, mL/min/ 1.73 m^2	3.24 (1.76, 5.52)	2.87 (1.49, 4.91)	3.52 (1.88, 5.67)	3.16 (1.61, 5.31)	< .05
WBC, × 10^9/L	5.73 (4.50, 7.20)	5.50 (4.40, 7.10)	5.73 (4.56, 7.17)	6.30 (4.49, 8.17)	> .05
Hemoglobin, g/L	78.86 ± 16.65	78.35 ± 17.51	79.67 ± 16.47	75.80 ± 14.73	> .05
Platelet, × 10^9/L	161 (118, 207)	109 (83, 143)	176 (142, 214)	232 (190, 298)	< .001
Lymphocyte, × 10^9/L	1.11 (0.86, 1.41)	1.31 (1.04, 1.67)	1.09 (0.86, 1.34)	0.72 (0.52, 0.88)	< .001
Albumin, g/L	35.44 ± 5.22	35.98 ± 5.27	35.39 ± 5.14	34.17 ± 5.32	< .05
Uric Acid, mmol/L	446.47 ± 131.94	443.83 ± 134.28	445.42 ± 130.03	459.97 ± 136.38	> .05
Total Cholesterol, mmol/L	4.09 (3.37, 4.89)	3.92 (3.19, 4.72)	4.12 (3.40, 4.99)	4.27 (3.58, 4.95)	< .05
TG, mmol/L	1.27 (0.90, 1.77)	1.23 (0.83, 1.65)	1.27 (0.91, 1.85)	1.32 (0.94, 1.80)	> .05
HDL-C, mmol/L	1.10 (0.90, 1.40)	1.12 (0.89, 1.40)	1.09 (0.90, 1.37)	1.11 (0.95, 1.47)	> .05
Apo-A1	1.23 (1.08, 1.41)	1.27 (1.10, 1.46)	1.22 (1.07, 1.40)	1.20 (1.02, 1.36)	> .05

Abbreviations: PLR, platelet-to-lymphocyte ratio; CVD, cardiovascular disease; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol, Apo-A1, apolipoprotein-A1.

(low group: PLR < 108.33, medium group: PLR 108.33 to 257.50 and high group: PLR > 257.50). Patients in the high PLR group were more likely to be older than patients in the low PLR group, who were more likely to be male and had a longer PD duration. The primary etiology of ESRD was chronic glomerulonephritis in all three groups. There were significantly more patients with diabetes mellitus in the high PLR group than in the low PLR group ($c^2 = 11.27$, $P < .05$). However, the number of patients with CVD and a smoking status was not different among the three groups. As PLR values increased, the absolute lymphocyte count decreased, while the absolute platelet counts increased. Similarly, the levels of albumin and total cholesterol and the eGFR in the high PLR group were significantly higher than those in the low PLR group ($P < .05$, $P < .05$, $P < .05$; respectively). There were no meaningful differences in BMI, systolic pressure, total Kt/V, white blood cells, hemoglobin, uric acid, TG, HDL-C or Apo-A1 among the groups.

Associations Between the PLR and All-Cause Mortality

During the median follow-up period of 27.5 months (IQR: 13.6 to 41.6 months), there were 148 (15.8%) patients transferred to HD, 56 (6.0%) patients received kidney transplants, 25 (2.7%) patients dropped out of the cohort, and a total of 221 (23.5%) patients died. Of these 221 patients, 114 (51.6%) deaths were attributed to cardiovascular mortality, 19 (8.6%) to infectious diseases, 20 (9.0%) to cachexia, 3 (1.4%) to malignancy, 21 (9.5%) to other reasons and 44 (19.9%) to unknown reasons.

Kaplan-Meier estimates of survival for patients with different PLR levels are shown in Figure 2. Patients in the high PLR group had a higher mortality rate than patients in the low PLR group (log rank = 13.75, $P < .001$). The 1-year and 3-year overall survival rates were 88.9% and 71.7%, respectively, for patients in the high PLR group compared with 98.6% and 86.2%, respectively, for patients in the low PLR group. Cox regression analysis was used to determine the relationship between platelet, lymphocyte and PLR levels and all-cause mortality. As shown in Table 2, the HR (and 95% CI) of all-cause mortality in the high PLR group was 2.15 (1.42 to 3.26, $P < .001$) compared with that in the low PLR group. After adjusting for age, sex, diabetes, history of CVD, systolic blood pressure, smoking, white blood cells, hemoglobin, serum albumin, total cholesterol, HDL-C and Apo-A1, the mortality rate was higher in the high PLR group than in the low PLR group (HR = 1.64, 95% CI: 1.02 to 2.63, $P < .05$). These results suggest that neither platelets nor lymphocytes were correlated with either parameter in models 1 to 3 (Table 2).

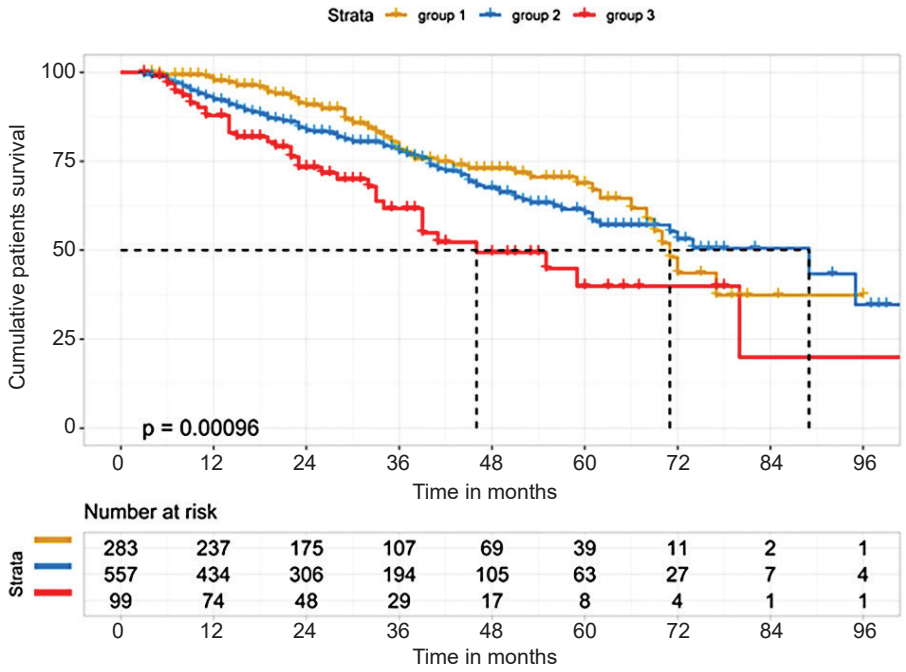

Figure 2. Survival Curves for Patients Stratified by Platelet-to-Lymphocyte Ratio

Table 2. The Associations of Platelet, Lymphocyte and the PLR with All-Cause Mortality

Variables	Platelet		Lymphocyte		PLRa	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Unadjusted	1.002 (1.000 to 1.004)	< .05	0.94 (0.70 to 1.26)	> .05	2.15 (1.42 to 3.26)	< .001
Model 1	1.001 (1.000 to 1.003)	> .05	1.007 (0.78 to 1.31)	> .05	1.57 (1.03 to 2.39)	< .05
Model 2	1.001 (0.999 to 1.003)	> .05	1.02 (0.77 to 1.36)	> .05	1.55 (1.01 to 2.38)	< .05
Model 3	1.000 (0.998 to 1.003)	> .05	0.86 (0.60 to 1.23)	< .05	1.64 (1.02 to 2.63)	< .05

Abbreviations: PLR, platelet-to-lymphocyte ratio; HR, hazard ratios; 95% CI, 95% confidence intervals.
Model 1: Adjusted for Age, Sex
Model 2: Model 1 Adjusted for Diabetes, History of CVD, Systolic Blood Pressure, Smoking
Model 3: Model 2 Adjusted for WBC, Hemoglobin, Serum Albumin, Total Cholesterol, HDL cholesterol, Apolipoprotein A1
[a]The High PLR Versus the Low PLR

DISCUSSION

According to the recently study, we found that the PD as a treatment of glomerular disease is increased rapidly and become more and younger in central area of china.[23] ESRD patients bear a considerable risk of total and cardiovascular death. Our study found that during the median follow-up period of 27.5 months, a total of 221 (23.5%) patients died, which indicated that PD patients had a poor chance of survival. This result was consistent with other previous studies [24,25], which underscores the need for defining reliable prognostic factors for PD patients in order to help identify patients at high risk of death and to devise effective preventive strategies.

In our study, we demonstrated that the PLR value was a useful biomarker for predicting the clinical course of PD patients. Unsurprisingly, our study found that the PLR may act as an independent predictor of all-cause mortality in PD patients. In addition, we also found that patients with a higher PLR had a higher mortality risk. The 1-year and 3-year overall survival rates were 88.9% and 71.7% for patients in the high PLR group compared with 98.6% and 86.2% for patients in the low PLR group, respectively.

The PLR was calculated as the ratio of platelets to lymphocytes in peripheral blood, and this value has been widely used as a marker of systemic inflammation.[20] Growing evidence has shown that the PLR, as a novel inflammatory marker, is associated with all-cause mortality in cardiac and noncardiac disorders.[13,19,26] Azab *et al.*[27] showed that a higher PLR was associated with higher 4-year all-cause mortality rates in patients with non-ST-elevation myocardial infarction. Similarly, Lee *et al.*[13] demonstrated that an elevated PLR was associated with all-cause mortality in patients at high risk of coronary artery disease who underwent coronary angiography; the PLR may be a useful prognostic biomarker in this population. Furthermore, Yaprak *et al.*[19] showed that the PLR was an independent predictor of all-cause mortality and that a higher PLR was associated with a higher mortality risk in HD patients. Consistent with these studies, we also found that a higher PLR was associated with a higher mortality risk and that it may act as an independent predictor of all-cause mortality in PD patients. However, the actual mechanisms underlying how the PLR affects survival in PD patients are unclear. There are some potential explanations. First, an increased inflammatory response may be one of the possible mechanisms. A previous study showed that platelets could interact with various inflammatory cell types, including lymphocytes, neutrophils, and mononuclear phagocytes[28] and that the interactions of platelets with these cells mentioned above might initiate and exacerbate inflammation in the arterial wall. Moreover, chronic inflammation, which is highly prevalent in ESRD patients, is associated with a high mortality rate in dialysis patients.[29] Furthermore, during inflammation, a variety of inflammatory mediators, such as interleukins (e.g., IL-1, IL-3, and IL-6), are released that stimulate megakaryocytes to proliferate and increase platelet levels in the circulation.[30] Activated platelets promote a proinflammatory environment by secreting cytokines and coagulation factors, and they play a key role in the initiation and progression of atherosclerosis.[31] Therefore, it has been demonstrated that increased platelets may be an important aspect of increased atherosclerosis, especially in the area of inflammation.[32,33] Moreover, atherosclerosis plays a pivotal role in the progression of CVD, which is one of the leading causes of death among ESRD patients.[34] Finally, a higher

PLR represents not only increased platelets but also decreased lymphocytes. A previous study indicated that low lymphocyte levels represented a depressed immune response that is associated with adverse outcomes.[35] Thus, these mechanisms might be related to the PLR and mortality among PD patients. However, the exact mechanisms need to be further elucidated in future studies. In addition, although previous studies have shown that higher platelet and lower lymphocyte counts are associated with poor clinical outcomes in various diseases;[36,37] our study found that neither platelets nor lymphocytes were associated with all-cause mortality in PD patients. Therefore, the PLR may be a prognostic marker superior to either individual platelet or lymphocyte counts due to the following potential reasons. First, compared with individual platelet or lymphocyte counts, the PLR is relatively more stable and is less likely to be altered by different physiologic and pathologic conditions. Second, the ratio may be able to reduce the overall biological variability in the dataset and may cancel out the systematic errors, thus increasing statistical power and reducing noise in the dataset.[38] Last but not least, an elevated PLR may suggest a predictive risk of both increased platelet and decreased lymphocyte counts. Compared with many other measures of inflammatory markers, such as C-reactive protein, the PLR is also inexpensive, easily calculated and readily available upon admission and therefore adds no additional cost; thus, the PLR might be useful as a predictor of mortality risk in PD patients. Our study has several limitations. First, the current study is a retrospective study, which can only reveal associations and not causality. Second, all of the parameters were measured on a single occasion at baseline, not taking into account changes during the follow-up period. If there had been a latent infection or inflammation at that time, the results could have been affected. Third, given the exclusion criteria aimed at eliminating factors that independently affect platelet and lymphocyte counts, the utility of the PLR may be limited to a selective population of patients. Fourth, because of the limited sample size, there is a possibility of residual confounding from variables that were not measured, even after the adjustment for the clinical variables. Our future studies will address these issues.

CONCLUSION

Our study demonstrates that the PLR is associated with long-term all-cause mortality in PD patients and could be a significant, independent predictor of long-term all-cause mortality in this population.

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None.

DISCLOSURE STATEMENT

The authors have no conflicts of interest to declare.

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Correspondence to:
Yu Wang, MD
Department of Nephrology, The First Affiliated Hospital of Nanchang University, 17# Yongwai Street, Nanchang 330006, China.
Tel: 0086 791 8869 2515
Fax: 0086 791 8869 3353
E-mail: smilife@163.com

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