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Prognostic value of lymphocyte cell ratios in peritoneal dialysis

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ABSTRACT

Background: Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been introduced as useful inflammatory markers to predict the outcome of a wide spectrum of diseases, such as malignancies and cardiovascular pathologies. Limited evidence is available for their role in end-stage renal disease and dialysis patients. The aim of this study was to evaluate NLR and PLR as predictors of mortality in peritoneal dialysis (PD) patients. **Methods:** In this retrospective study 122 incident PD patients between 2004 and 2019 were included. Demographic, clinical and laboratory data were collected. Relationships between NLR, PLR and high-sensitivity C-reactive protein (hs-CRP) were evaluated by Spearman correlation test. Univariable and multivariable Cox regression analysis were performed to determine the association of NLR and PLR with all-cause mortality. **Results:** Mean levels of NLR and PLR were 3.99±2.6 and 195.5±101.7, respectively. Both NLR and PLR were significantly and positively correlated with serum hs-CRP levels (r=0.340, p<0.001 and r=0.360, p<0.001, respectively). The overall mortality rate was 18.9% after a mean follow-up of 30.2±24.0 months. On multivariable modeling, we found that higher NLR (HR=1.662, 95%CI 1.117-2.472) and higher PLR (HR=1.010, 95%CI 1.004-1.015), in addition to lower residual renal function and higher Charlson comorbidity index were significant independent predictors of poor survival, when adjusted for nutritional status. **Discussion:** In this study, NLR and PLR were validated as inflammatory markers and predicted survival in our PD patients. Our results suggest that NLR might be a better indicator of mortality than PLR.

Key-words: Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, inflammation, mortality.

INTRODUCTION

Chronic inflammation plays an important role in the development and progression of various chronic conditions and diseases such as obesity, diabetes, cardiovascular disease, cancer, chronic obstructive lung disease and chronic kidney disease (CKD)[1–3]. Patients with CKD tend to have elevated levels of inflammatory mediators, which accelerates the progression of atherosclerosis, the most important cause of morbidity and mortality in CKD[4].

In addition to known conventional indicators of inflammation such as C-reactive protein (CRP), fibrinogen, erythrocyte sedimentation rate and several interleukins, studies have shown that neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), readily available biomarkers calculated from complete blood count (CBC), are also increased during inflammation and have been used as prognostic factors in cardiovascular and oncologic diseases[5,6].

Recent studies have indicated that NLR and PLR offer a plausible strategy in clinical practice for evaluation of inflammation in end-stage renal disease (ESRD) and may predict mortality among patients with CKD, including hemodialysis patients[7–10]. However, their prognostic value in PD is still unknown. The aim of this study was to evaluate NLR and PLR as predictors of all-cause mortality in PD patients.

METHODS

Study population

We retrospectively examined data from all ESRD patients aged ≥ 18 years who initiated PD at the Centro Hospitalar Universitário do Algarve from January 1, 2004 to April 30, 2019 and who had a peritoneal equilibration test (PET). They were treated with continuous ambulatory PD or automated PD. Patients were followed up from the first date of dialysis until death, kidney transplantation, loss to follow-up or the date of final follow-up assessment for all patients (April 30, 2019).

Clinical and biochemical data at the time of PET were recorded, including age, Charlson comorbidity index (CCI), pre-albumin as marker of nutritional status, normalized glomerular filtration rate (nGFR) and presence of diabetes mellitus. Blood samples for CBC and biochemistry panels were collected for each patient early in the morning before the first exchange of day and immediately analyzed in our hospital laboratory. For CBC analysis, an automatic blood counter was used. NLR was calculated using neutrophil count divided by lymphocyte count whereas PLR was calculated using platelet count divided by lymphocyte count, both obtained from the same automated blood sample. Weekly Kt/V urea was determined by adding renal Kt (24-hour urine urea nitrogen content/serum urea nitrogen) and peritoneal Kt (24-hour dialysate urea nitrogen content/serum urea nitrogen) normalized to the patient's estimated urea distribution volume (V).

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Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous parametric variables as mean and standard deviations (SD). Normal distribution was checked using skewness and kurtosis. Correlations between NLR, PLR and serum high-sensitivity C-reactive protein (hs-CRP) were evaluated using the Spearman correlation test. Adjusted survival curves were estimated using the Cox average method. A backward elimination procedure based on likelihood ratio was then carried out to remove superfluous variables from the model until the most parsimonious model was identified. Data were analyzed using the software package Statistical Package for the Social Science (SPSS) 23.0 for Windows. P-values less than 0.05 were considered significant.

RESULTS

Patient characteristics

A total of 164 incident patients started PD during the study period, but only 122 had a PET and were included. The mean age and CCI was 55.0±17.5 years and 5.0±2.5 respectively, of whom 54.9% were male, 93.4% were caucasian and 31.1% were diabetic. PETs were performed within the first 4.9±7.2 months and the mean follow-up was 30.2±24.0 months. During this period of follow-up, 52 (42.6%) patients were transferred to long-term hemodialysis, 21 (17.2%) received kidney transplants and 3 (2.5%) dropped out of the cohort. A total of 22 (18%) patients died during the course of the study. Our population was dialyzed with a mean Kt/V 2.75±0.94 and a mean creatinine clearance 101±43.3L/week/1.73m^2, and the mean evaluated parameters were nGFR 6.7±4.7 ml/min/1.73m2, prealbumin 39.3±113 mg/dL, hs-CRP 10.99±14.97mg/L, neutrophils 5.6±2.5x10^9/L, lymphocytes 1.8±2.3x10^9/L, and platelets 269.6±86.5x10^9/L. Corresponding values for NLR and PLR were 3.99±2.6 and 195.5±101.7, respectively. Patients' demographic, clinical and laboratory features are presented in Table I.

Table I

Demographic, clinical and laboratory features of the study group

Parameters	PD patients (n = 122)
Age, years	55.0 ± 17.5
Male gender, n (%)	67 (54.9%)
Caucasian, n (%)	114 (93.4%)
Diabetic, n (%)	38 (31.1%)
Renal diagnosis (%)	
Diabetic nephropathy	24.6%
Chronic glomerulonephritis	17.2%
Hypertensive nephrosclerosis	9.0%
Other / Unknown etiology	49.2%
CCI	5.0 ± 2.5
Hemoglobin (g/dL)	12.3 ± 1.9
Absolute neutrophil count (x10^9/L)	5.6 ± 2.5
Absolute lymphocyte count (x10^9/L)	1.8 ± 2.3
Absolute platelet count (x10^9/L)	269.6 ± 86.5
NLR	3.99 ± 2.6
PLR	195.5 ± 101.7
hs-CRP (mg/L)	10.99 ± 14.97
nGFR (mL/min/1.73m^2)	6.7 ± 4.7
Pre-albumin (mg/dL)	39.3 ± 113
D/P creatinine ratio	0.6 ± 0.12
Creatinine clearance (L/week/1.73m^2)	101.3 ± 43.3

Values are means ± SD, unless specified otherwise. CCI = Charlson comorbidity index; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; hs-CRP = high sensitivity C-reactive protein; nGFR = normalized glomerular filtration rate; D/P creatinine ratio = dialysate to plasma creatinine ratio.

Association between NLR, PLR and hs-CRP levels

PLR was significantly and positively correlated with serum hs-CRP levels (r=0.360, p<0.001). Similarly, NLR was also significantly and positively correlated with serum hs-CRP levels (r=0.340, p<0.001).

Mortality Predictability Comparisons of Selected Laboratory Variables

On univariable Cox regression modeling, higher NLR, higher PLR, lower nGFR and higher CCI were significantly associated with risk of overall mortality. Separate models were performed for NLR and PLR associated factors. On both multivariable modeling, higher NLR and higher PLR, in conjunction with lower nGFR and higher CCI were significant independent predictors of poor survival, adjusting for prealbumin levels as a nutritional indicator (Table II and III).

Table II

Multivariable Cox regression analysis for NLR levels showing important predictors for overall mortality in PD patients.

Independent variables	All-cause mortality	
	Hazard ratio (95% CI)	P value
nGFR	0.706 (0.554-0.900)	0.005
Pre-albumin	1.023 (0.974-1.074)	0.365
CCI	1.650 (1.174-2.320)	0.004
NLR (> mean vs. ≤ mean)	1.662 (1.117-2.472)	0.012

nGFR = normalized glomerular filtration rate; CCI = Charlson comorbidity index; NLR = neutrophil-to-lymphocyte ratio.

Table III

Multivariable Cox regression analysis for PLR levels showing important predictors for overall mortality in PD patients.

Independent variables	All-cause mortality	
	Hazard ratio (95% CI)	P value
nGFR	0.673 (0.513-0.883)	0.004
Pre-albumin	1.023 (0.977-1.071)	0.332
CCI	1.827 (1.284-2.600)	0.001
PLR (> mean vs. ≤ mean)	1.010 (1.004-1.015)	0.001

nGFR = normalized glomerular filtration rate; CCI = Charlson comorbidity index; PLR = platelet-to-lymphocyte ratio.

DISCUSSION

Chronic inflammation is defined as a part of malnutrition-inflammation-atherosclerosis syndrome in patients with CKD and ESRD, leading to a considerable risk of total and cardiovascular death[11]. In this current study, 18.9% of patients died after a mean of follow-up time of 30 months, indicating a high risk of poor outcome in chronic dialysis patients. Similar outcomes have also been reported by other cohorts of PD patients, which underscores the need for additional parameters for risk stratification in PD patients[12].

NLR and PLR, simple ratios obtained from a universally available low-cost complete blood count test routinely performed on admission, have been widely used as biomarkers of systemic inflammation[13,14]. Neutrophils may secrete a number of cytokines and activate other immune cells, thus promoting low-grade inflammation in the arterial wall[15]. On the other hand, studies demonstrated that activated platelets could incite leukocyte recruitment to the vessel wall and trigger the inflammation that can mainly be seen in the pathogenetic mechanism of atherosclerosis[16,17]. NLR was found to be significantly correlated with inflammatory markers, including CRP, pentraxin-3, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in a population receiving renal replacement therapy[18]. PLR was also positively correlated with NLR ratio, IL-6 and TNF-α levels. Additionally, ESRD patients with higher PLR values had higher levels of inflammation[19]. Our study findings were confirmatory to previous studies in regard to positive correlation between NLR and PLR with serum hs-CRP levels[20,21].

Catabay C. et al. conducted a large-scale study including 108,548 hemodialysis patients which showed that high NLR value, but not PLR, provided additional benefit in predicting mortality[10]. Lu X. et al. enrolled 86 patients undergoing PD and suggest that high NLR is independently associated with arterial stiffness and predicts cardiovascular and all-cause mortality[22]. In our multivariate Cox regression analysis, NLR and PLR were found to be significant predictors of all-cause mortality in PD patients. Furthermore, this relationship was independent of various confounding factors, including CCI, nGFR and pre-albumin. Our results also showed the excellent predictive value found for CCI and nGFR, in line with preceding evidence[23,24]. On the other hand, the lower predictive value found for pre-albumin may be related to the high standard deviation of our data.

Several limitations of this study should be considered. First, it was a small-sample observational, retrospective, single-institution study, which only enrolled 122 patients and thus may have weakened the power of some statistical analysis. Second, all the parameters were measured on a single occasion at the time of PET and did not take into account changes over time. Third, we did not look at medical conditions or treatments known to affect the CBC. Nevertheless, we collected data at the time of PET, eliminating possible confounding factors, such as infection, since this condition is a contraindication to perform this test, according to our unit protocol. Fourth, the current study is a prognostic rather than an etiologic study. Also, we only used serum hs-CRP as an inflammatory marker to correlate with NLR and PLR and, although statistically significant, these correlations are considered weak.

The findings of the present study indicated that baseline NLR and PLR measurements may provide a simple and inexpensive method for predicting mortality in chronic PD patients, when compared with other prognostic markers which may need specific equipment or reagent. Our analysis also suggests that NLR can predict mortality better than PLR in this population. Prospective studies are needed to investigate the potential prognostic impact of those markers.

Authors' contribution

Authorship of RCM. ECC, ATD and AMG provided clinical assistance, made a substantial contribution to the concept and design of the work and revised it critically for important intellectual content. IB provided clinical assistance. PLN revised it critically for important intellectual content. All authors approved the final manuscript.

Disclosure of potential conflicts of interest: none declared.

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