Clin. Lab. 2021;67:XXX-XXX

ORIGINAL ARTICLE

Predictive Value of Peripheral Blood Neutrophil-To-Lymphocyte Ratio and Platelet-To-Lymphocyte Ratio on Patient Survival with Peritoneal Dialysis

Ling-Cang Xu [1, 2], Fang-Fang Zhou [1, 2], Meng Li [1, 2], Zhi-Wei Dai [1, 2], Ke-Dan Cai [1, 2], Bei-Xia Zhu [1, 2], Qun Luo [1, 2]

[1] *Department of Nephrology, Hwa Mei Hospital, University of Chinese Academy of Sciences, Ningbo, Zhejiang Province, China*
[2] *Ningbo Institute of Life and Health Industry, University of Chinese Academy of Sciences, Ningbo, Zhejiang Province, China*

SUMMARY

Background: **This study is to explore the predictive value of peripheral blood neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) on the prognosis of patients with peritoneal dialysis (PD).**
Methods: **A total of 378 patients who underwent PD from July 2004 to November 2019 were selected as the research subjects. According to whether death occurred during the follow-up period, they were divided into death group (86 cases) and survival group (292 cases). The differences in clinical indicators between the two groups were compared, and the multivariate Cox regression model and receiver operating characteristic curve (ROC) were used to analyze and summarize the factors affecting the prognosis of PD patients.**
Results: **Compared with the survival group, there were significant differences in age, lymphocytes, NLR, PLR, and combined cerebrovascular disease between the death group and the survival group ($p < 0.05$). Multivariate Cox regression analysis showed that advanced age (HR = 1.055, 95% CI: 1.038 - 1.072), increased NLR (HR = 1.136, 95% CI: 1.067 - 1.210), and increased PLR (HR = 1.184, 95% CI: 1.018 - 3.026) were risk factors for all-cause death in PD patients. The results showed that the area under the ROC curve (AUC) of NLR and PLR for predicting all-cause death of PD patients were 0.698 and 0.659, respectively, the sensitivity was 69.77%, and the specificity was 66.78% and 58.56%, respectively. The optimal critical values were NLR ≥ 3.71 and PLR ≥ 149.28. Taking the best cutoff value of the ROC curve as the threshold, it showed that the cumulative survival rate of patients with NLR ≥ 3.71 was significantly lower than that of patients with NLR < 3.71 (Log rank χ^2 = 37.551, p = 0.000). It also showed that the cumulative survival rate of patients with PLR ≥ 149.28 was lower than that of patients with PLR < 149.28 (Log rank χ^2 =23.686, p = 0.000).**
Conclusions: **NLR and PLR have a good predictive effect on the prognosis of PD patients.**
(Clin. Lab. 2021;67:xx-xx. DOI: 10.7754/Clin.Lab.2021.210124)

Correspondence:
Qun Luo
Department of Nephrology
Hwa Mei Hospital
University of Chinese Academy of Sciences
No. 41, Northwest Street
Ningbo, Zhejiang Province, 315010
China
Phone/Fax: +86 574-83870217
Email: luoqun@ucas.ac.cn

Manuscript accepted March 1, 2021

KEY WORDS

peripheral blood, neutrophils/lymphocytes, platelets/lymphocytes, peritoneal dialysis, prognosis, prediction

INTRODUCTION

Chronic kidney disease (CKD) results from structural and functional changes caused by various reasons. It is one of the global public health problems and eventually developing into end-stage renal disease [1]. Peritoneal

dialysis (PD) has the advantages of low price, simple operation, little hemodynamic impact, and good protection of residual renal function. It has become an important means of renal replacement therapy for end-stage renal disease [2,3]. At present, the clinical prognosis of PD patients is poor, and the factors affecting the prognosis are complex. Among them, cardiovascular disease and peritonitis are the two main influencing factors, which have received widespread attention [4,5]. There are only few potential predictable indexes, for example C reactive protein for the clinical prognosis of patients with PD complicated by cardiovascular disease. However, the majority of increased CRP levels occurred in PD patients without an obvious cause. Moreover, CRP levels vary over time in the same patient, from normal to high or from high to normal, for no obvious reason [6].

Neutrophil/lymphocyte ratio (NLR) is a new type of inflammatory marker, which is closely related to the clinical prognosis of acute heart failure. NLR is significantly increased when PD is complicated by cardiovascular disease. It has become one of the effective monitoring indicators for cardiovascular disease in PD patients [7]. Platelet/lymphocyte ratio (PLR) is an indicator of systemic inflammation, which can reflect the inflammatory state of patients with continuous ambulatory PD, as well as the inflammatory state of cardiovascular diseases, rheumatic immune diseases, and other diseases, which are related to the clinical prognosis of patients with these diseases [8]. However, there are few reports on the predictive value of NLR and PLR on the clinical prognosis of patients with PD complicated by cardiovascular disease. Based on this, this study explored the relationship between NLR, PLR, and the clinical prognosis of PD patients, and provides references for the clinical prevention and treatment of the disease.

MATERIALS AND METHODS

Patients

A total of 378 patients who underwent PD treatment in the Department of Nephrology, Hwa Mei Hospital, University of Chinese Academy of Sciences from July 2004 to February 2020 were selected as the research subjects. Inclusion criteria: (1) age ≥ 18 years; (2) dialysis period ≥ 3 months. Exclusion criteria: combined with hematological diseases, malignant tumors, liver cirrhosis or severe liver insufficiency, active autoimmune disease, severe arrhythmia, acute myocardial infarction, chronic obstructive pulmonary disease, recent severe infection, lack of neutrophils, platelets, lymphocytes, and other important information.

Data collection

The medical record management system was used to collect baseline clinical data of all patients before starting PD, including age, gender, primary disease, complications, dialysis age, white blood cells, lymphocytes, neutrophils, platelets, serum albumin, (blood) total cholesterol, (blood) triglycerides, neutrophil-to-lymphocyte ratio (NLR) = neutrophil/lymphocyte, platelet-to-lymphocyte ratio (PLR) = platelet/lymphocyte.

Follow-up and the endpoint

All patients except those who died or were transferred to kidney transplantation or hemodialysis were followed up from the start of PD treatment until February 29, 2020. For the patients who died from various causes, the survival time and cause of death were recorded. For those patients who survived, the time to kidney transplantation or hemodialysis were recorded.

Statistical analysis

SPSS 22.0 software was used for statistical analysis. The measurement data conforming to the normal distribution was represented by ($\overline{x} \pm s$), the two-sample *t*-test was used for the comparison of normally distribution data, and the Mann-Whitney U test was used for the comparison of non-normally distribution data. The count data was expressed as rate, and compared with χ^2 test. The Cox proportional hazard regression model was used to analyze the independent risk factors of all-cause death in patients, and ROC curve and Youden index were used to evaluate the predictive value of NLR and PLR for all-cause death in PD patients, and the optimal critical value for prediction was determined. The survival analysis was performed using Kaplan-Meier method. $p < 0.05$ indicates that the difference is statistically significant.

RESULTS

Outcomes and causes of death analysis

A total of 378 cases were enrolled in this study, included 206 males (54.5%) and 172 females (45.5%). The average age was 61.63 ± 16.32 years old. There were 79 cases of smoking (20.9%), 50 cases of alcohol drinking (13.2%), 334 cases of hypertension (88.4%, included 209 cases of primary hypertension, 125 cases of renal hypertension), 120 cases of diabetes (31.7%, included 3 cases of type 1 diabetes and 117 cases of type 2 diabetes), 61 cases of heart disease (16.1%), and 41 cases of cerebrovascular disease (10.8%). The period of dialysis was 3 to 155 months, and the median period of dialysis was 25 months. At the end of the follow-up, 86 patients died. Among the 292 surviving patients, 223 cases maintained PD (76.3%), 47 cases were converted to hemodialysis (16.1%), and 22 cases received kidney transplantation (7.5%).

Comparison of clinical characteristics between the two groups

There were no significant differences in gender, heart rate, smoking, alcohol drinking, combined hypertension, combined diabetes, combined heart disease, triglycerides, total cholesterol, HDL-C, LDL-C between

Table 1. Comparison of basic information.

Indicators	Death group (n = 86)	Survival group (n = 292)	t/χ^2	p-value
Age (years, $\bar{x} \pm s$)	73.16 ± 13.58	58.24 ± 15.50	8.061	0.000
Gender (male/female, n)	48/38	158/134	0.03	0.860
Triglyceride (μmol/L)	1.77 ± 1.35	1.76 ± 1.82	0.06	0.952
Total cholesterol (μmol/L)	4.21 ± 1.06	4.28 ± 1.19	0.475	0.641
HDL-C (μmol/L)	1.07 ± 0.32	1.12 ± 0.38	0.966	0.343
LDL-C (μmol/L)	2.27 ± 0.87	2.38 ± 0.89	1.110	0.268
White blood cell count (x 10^9/L)	6.94 ± 2.42	6.18 ± 1.97	2.978	0.003
Neutrophil count (x 10^9/L)	4.98 ± 2.30	6.15 ± 1.95	4.688	0.000
Lymphocyte count (x 10^9/L)	1.03 ± 0.42	1.28 ± 0.47	4.582	0.000
Platelet count (x 10^9/L)	189.71 ± 68.06	182.46 ± 63.95	0.915	0.362
NLR	6.13 ± 5.75	3.67 ± 2.12	3.867	0.000
PLR	227.68 ± 204.39	156.64 ± 75.72	3.172	0.002
Heart rate (beats/min)	78.84 ± 10.31	78.87 ± 11.23	0.024	0.981
BMI (kg/m^2)	21.96 ± 3.45	22.65 ± 3.67	1.538	0.125
Peritoneal dialysis time (months)	32.41 ± 28.52	36.76 ± 30.42	1.182	0.238
Smoking history (none/yes)	67/19	232/60	0.096	0.757
Alcohol drinking history (none/yes)	74/12	254/38	0.051	0.821
Hypertension			3.367	0.186
None	13	31		
Primary	51	158		
Renal	22	103		
Diabetes			1.233	0.543
None	57	201		
Type I	0	3		
Type II	29	88		
Heart disease (none/yes)	67/19	250/42	2.918	0.088
Cerebrovascular disease (none/yes)	71/15	266/26	5.008	0.025

Table 2. Multivariate Cox regression risk analysis of all-cause death in peritoneal dialysis patients.

Variables	B	SE	Wald χ^2	p-value	HR	HR 95% CI
NLR	0.127	0.032	15.580	0.0001	1.136	1.067 - 1.210
PLR	0.169	0.035	23.315	< 0.0001	1.184	1.018 - 3.026
Age	0.054	0.008	42.113	< 0.0001	1.055	1.038 - 1.072
Cerebrovascular disease	0.477	0.287	2.769	0.0961	1.612	0.921 - 2.819

the two groups ($p > 0.05$). Compared with the survival group, the death group had statistically significant differences in age, lymphocytes, white blood cell count, neutrophils, NLR, PLR, and combined cerebrovascular disease ($p < 0.05$), see Table 1.

Multivariate Cox regression analysis of influencing factors affecting the clinical outcome of patients

According to the results of univariate analysis, survival/death (0/1) was used as the dependent variable. The neutrophil count, white blood cell count, lymphocytes and NLR, PLR were collinear. Therefore, age, NLR,

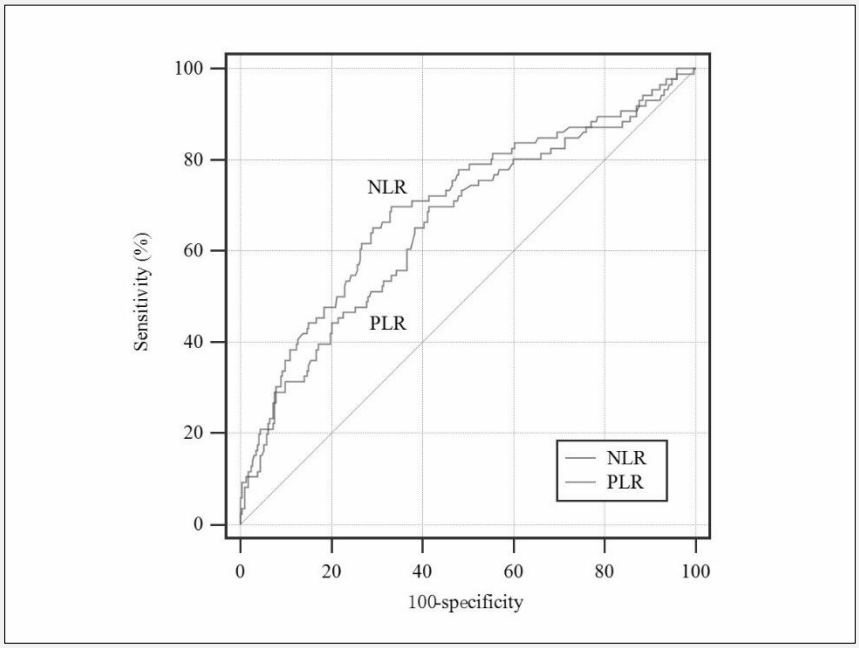

Figure 1. The ROC curve of NLR and PLR for the prognosis of peritoneal dialysis patients.

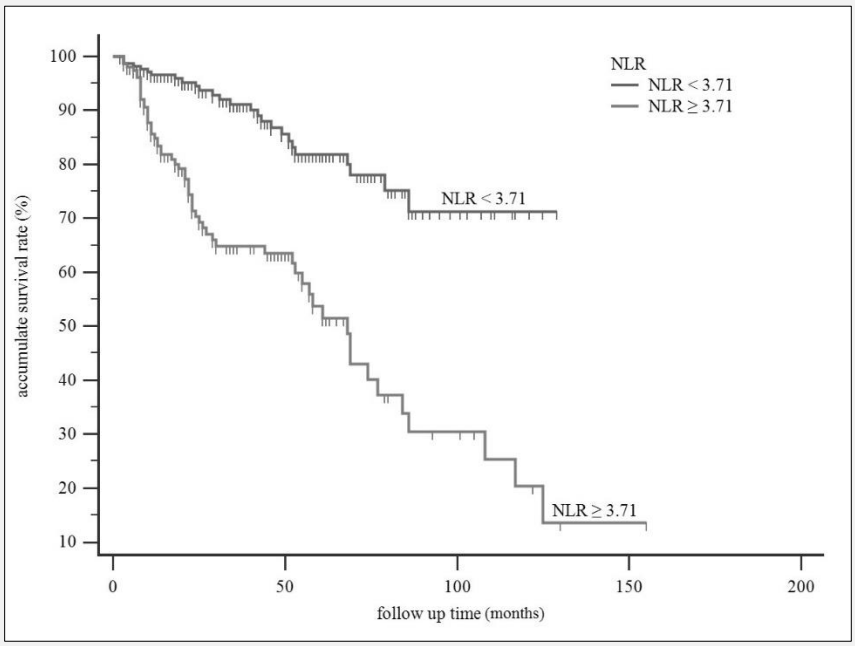

Figure 2. Survival analysis results of peritoneal dialysis patients with different NLR levels.

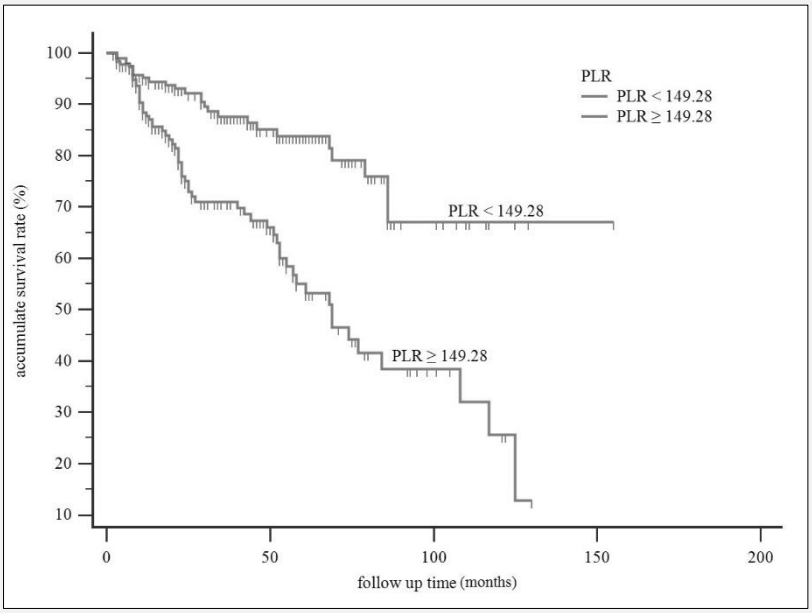

Figure 3. Survival analysis results of peritoneal dialysis patients with different PLR levels.

PLR, and combined cerebrovascular disease were included as independent variables for multivariate Cox regression analysis. The results showed that advanced age and increased NLR and PLR were risk factors for all-cause death in PD patients, as shown in Table 2.

ROC curve analysis of NLR and PLR in predicting all-cause death in PD patients

The ROC curve results showed that the area under the ROC curve (AUC) for NLR predicting all-cause death in PD patients was 0.698 (95% CI: 0.649 - 0.744). The optimal critical value predicted by NLR was 3.71. When this cutoff value was used to predict all-cause death in patients, the sensitivity was 69.77% and the specificity was 66.78%. The AUC of PLR predicting all-cause death in PD patients was 0.659 (95% CI: 0.609 - 0.707), and the best cutoff value was 149.28. When this cutoff value was used to predict all-cause death in patients, the sensitivity was 69.77%, and the specificity was 58.56% (Figure 1).

Survival analysis results of PD patients with different levels of NLR and PLR

According to the ROC curve results, with NLR = 3.71 as the threshold, they were divided into high NLR group (158 cases) and low NLR group (220 cases). The average survival time of the two groups was 70 (95% CI: 57 - 82) months and 106 (95% CI: 98 - 114) months, respectively. The results of survival analysis showed that the cumulative survival rate difference between the high NLR group and the low NLR group was statistically significant (Log rank χ^2 = 37.551, p = 0.000, HR = 3.767, 95% CI: 2.437 - 5.822), and the prognosis of patients with high NLR was significantly worse than patients with low NLR (Figure 2).

Taking PLR = 149.28 as the threshold, they were divided into high PLR group (182 cases) and low PLR group (196 cases). The median survival time of the two groups was 72 (95% CI: 62 - 81) months and 121 (95% CI: 109 - 134) months, respectively. The results of survival analysis showed that the cumulative survival rate difference between the high PLR group and the low PLR group was statistically significant (Log rank χ^2 = 23.686, p = 0.000, OR: 2.950, 95% CI: 1.927 - 4.512), and the prognosis of patients with high PLR was significantly worse than that of patients with low PLR (Figure 3).

DISCUSSION

PD utilizes the semi-permeable membrane properties of the peritoneum to exchange water, electrolytes, and metabolites through peritoneal dialysate and circulating blood. Patients often have cardiovascular diseases [9]. Studies have shown that [10] cardiovascular complications of PD are the main factor affecting the prognosis of patients and the main cause of death in PD patients. It is reported that the mortality of patients with PD com-

plicated by cardiovascular disease accounts for 51.6% of all-cause deaths [9]. It is reported in the literature that improving the prognosis of PD complicated by cardiovascular disease can improve the clinical prognosis of patients with PD [11]. Therefore, exploring specific and sensitive indicators of cardiovascular disease in PD patients, and conducting early intervention and treatment are medical problems that clinical medical workers in the PD field urgently need to solve.

Micro-inflammation is very common in patients with maintenance PD, and the persistent micro-inflammatory state is closely related to complications such as cardiovascular disease and malnutrition in PD patients [12]. When PD patients are in a micro-inflammatory state, they induce adhesion molecules, activate complement and other pathways through the action of inflammatory factors, leading to atherosclerosis, heart valve calcification and myocardial hypertrophy, which in turn induces corresponding cardiovascular diseases [13]. It has been reported that the more severe the micro-inflammatory state of PD patients, the higher the incidence of cardiovascular calcification, and the increase of high-sensitivity C-reactive protein (hs-CRP) is an independent risk factor for heart valve calcification [14].

As a marker of human immune inflammation, NLR has increasingly been widely used. It reflects the inflammatory state of the body to a certain extent and is a predictor of cardiovascular disease. Liu et al. [15] showed that NLR is positively correlated with hs-CRP and N-terminal-brain natriuretic peptide in patients with myocardial infarction. The higher the NLR content, the more severe the symptoms of heart failure in patients, and the risk of recent cardiovascular adverse events also significantly increases. The retrospective analysis of Lu et al. [7] confirmed that the levels of NLR and CRP in PD patients with cardiovascular disease were significantly higher than those in healthy people and PD patients without cardiovascular disease. There was a significant positive correlation between NLR and CRP, indicating that NLR can effectively reflect the inflammatory response in PD patients with cardiovascular disease and is an effective indicator for monitoring cardiovascular disease. The results of this study showed that, compared with the PD survival group, the death group had statistically significant differences in age, lymphocytes, NLR, PLR, and combined cerebrovascular disease. Multivariate Cox regression analysis and ROC curve results showed the predictive effect of NLR on the clinical prognosis of PD patients.

Platelet is an acute-phase reactant. It participates in the process of atherosclerosis by actively releasing pro-inflammatory factors. It can also combine with endothelial cells and white blood cells to promote the release of inflammatory factors, initiate and aggravate the inflammatory response of the blood vessel wall. The increase of platelets in peripheral vascular disease, atherosclerotic heart disease, and other diseases are closely related to the clinical prognosis of patients [16]. Studies have found that PLR is positively correlated with inflammatory indicators such as interleukin-6 and tumor necrosis factor-α [17]. Other studies have also reported that PLR is significantly associated with the mortality of patients with end-stage renal disease [18]. Chen et al. [8] found that the number of neutrophils, urea nitrogen, blood creatinine, triacylglycerol, PLR, NLR, and hs-CRP in patients with continuous ambulatory PD were significantly higher than that of healthy people, and that PLR was positively correlated with platelets, urea nitrogen, blood creatinine, hs-CRP, and NLR. Therefore, PLR can be used as an effective indicator to evaluate the inflammatory state of patients with continuous ambulatory PD. In this study, the results suggested that PLR is an effective indicator to predict the clinical prognosis of PD patients.

In summary, NLR and PLR have a good predictive effect on the prognosis of PD patients. NLR and PLR are both a ratio, which is more stable than a single hematological index. It can overcome the effects of dehydration, excessive body fluids or sample processing on the absolute value of blood cells. Therefore, it may be more valuable than platelet or lymphocyte count in suggesting the micro-inflammatory state of patients with PD.

Funding:

This study was supported by Ningbo Technology and Public Welfare Foundation, China (Grant No. 2015 C50038) and Zhejiang Medical Science and Technology Research Foundation, China (Grant No. 2020KY258).

Declaration of Interest:

The authors declared that they have no conflicts of interest to this work.

References:

1. Padmanabhan A, Gohil S, Gadgil NM, Sachdeva P. Chronic renal failure: An autopsy study. Saudi J Kidney Dis Transpl 2017;28: 545-51 (PMID: 28540891).

2. Imani PD, Carpenter JL, Bell CS, Brandt ML, Braun MC, Swartz SJ. Peritoneal dialysis catheter outcomes in infants initiating peritoneal dialysis for end-stage renal disease. BMC Nephrol 2018; 19:231 (PMID: 30217181).

3. Fischer A. [Hemo- and peritoneal dialysis: what non-nephrologists should know]. Ther Umsch 2018;75:387-94 (PMID: 30880 624).

4. Lehmann FP, Cano Sc F. [Cardiovascular disease in pediatric patients under chronic peritoneal dialysis]. Rev Chil Pediatr 2017; 88:236-42 (PMID: 28542658).

5. Szeto CC, Li PK. Peritoneal Dialysis-Associated Peritonitis. Clin J Am Soc Nephrol 2019;14:1100-5 (PMID: 31068338).

6. Fine A. Relevance of C-reactive protein levels in peritoneal dialysis patients. Kidney Int 2002;61:615-20 (PMID: 11849404).

7. Lu X, Wang S, Zhang G, Xiong R, Li H. High Neutrophil-to-Lymphocyte Ratio is a Significant Predictor of Cardiovascular and All-Cause Mortality in Patients Undergoing Peritoneal Dialysis. Kidney Blood Press Res 2018;43:490-9 (PMID: 29627842).

8. Chen T, Yang M. Platelet-to-lymphocyte ratio is associated with cardiovascular disease in continuous ambulatory peritoneal dialysis patients. Int Immunopharmacol 2020;78:106063 (PMID: 318 35088).

9. Banshodani M, Kawanishi H, Moriishi M, Shintaku S, Tsuchiya S. Association between Dialysis Modality and Cardiovascular Diseases: A Comparison between Peritoneal Dialysis and Hemodialysis. Blood Purif 2020;49:302-9 (PMID: 31851981).

10. Mehrotra R, Devuyst O, Davies SJ, Johnson DW. The Current State of Peritoneal Dialysis. J Am Soc Nephrol 2016;27:3238-52 (PMID: 27339663).

11. Klinger M, Madziarska K. Mortality predictor pattern in hemodialysis and peritoneal dialysis in diabetic patients. Adv Clin Exp Med 2019;28:133-5 (PMID: 30156388).

12. Rašić S, Hadžović-Džuvo A, Rebić D, Valjevac A, Unčanin S. Endothelial dysfunction in uremic patients on continuous ambulatory peritoneal dialysis (CAPD). Bosn J Basic Med Sci 2011;11: 153-7 (PMID: 21875416).

13. Harmankaya O, Akalin N, Akay H, et al. Comparison of risk factors for cardiovascular disease in hemodialysis and peritoneal dialysis patients. Clinics (Sao Paulo) 2015;70:601-5 (PMID: 26375 560).

14. Tabibi H, As'habi A, Najafi I, Hedayati M. Prevalence of dynapenic obesity and sarcopenic obesity and their associations with cardiovascular disease risk factors in peritoneal dialysis patients. Kidney Res Clin Pract 2018;37:404-13 (PMID: 306196 96).

15. Liu Z, Nguyen Khuong J, Borg Caruana C, et al. The Prognostic Value of Elevated Perioperative Neutrophil-Lymphocyte Ratio in Predicting Postoperative Atrial Fibrillation After Cardiac Surgery: A Systematic Review and Meta-Analysis. Heart Lung Circ 2020;29:1015-24 (PMID: 32089488).

16. Qian SX, Gu JX, Guan QB, Zhang XL, Wang YP. Serum oxidative stress, inflammatory response and platelet activation in patients with vascular vertigo. J Biol Regul Homeost Agents 2019; 33:499-504 (PMID: 30945512).

17. Chawla A, Paraoan V, Rabiu R, et al. Determining the stress biomarker profile in patients undergoing total knee replacement and the relationship with outcome at 12 months. Knee 2019;26:1379-85 (PMID: 31575511).

18. Yaprak M, Turan MN, Dayanan R, et al. Platelet-to-lymphocyte ratio predicts mortality better than neutrophil-to-lymphocyte ratio in hemodialysis patients. Int Urol Nephrol 2016;48:1343-8 (PMID: 27118565).