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The advantage of the platelet-to-lymphocyte ratio over neutrophil-to-lymphocyte ratio as novel markers of erythropoietin resistance in hemodialysis patients

Prednost odnosa trombocita i limfocita nad odnosom neutrofila i limfocita kao novih markera rezistencije na eritropoetin kod bolesnika na hemodijalizi

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Abstract

Background/Aim. Inflammation is one of the common factors that contribute to erythropoiesis stimulating agents (ESA) treatment resistance in hemodialysis patients. Lately, it is assessed by using new markers of inflammation, which are platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR). Their association with this therapy has not been fully investigated. The aim of the study was to evaluate the relationship between PLR, NLR, and ESA hyporesponsiveness index (EHRI). **Methods.** The research was conducted as a cross-sectional study and included 90 hemodialysis patients, who underwent clinical and laboratory testing in the form of physical examination and biochemical analyses. In all patients, the EHRI calculation was performed. **Results.** It is shown that EHRI had a statistically significant positive correlation with PLR ($p < 0.01$) and a negative correlation with hemoglobin levels ($p < 0.01$). Significant differences for logarithmically converted values of EHRI and PLR ($p < 0.05$) were found but not for EHRI and NLR ($p = 0.13$). **Conclusion.** Research has shown that PLR, together with NLR, could be used in assessing not only inflammation but also erythropoietin resistance in hemodialysis patients.

Key words:
blood platelets; erythropoietin; inflammation; lymphocytes; neutrophils; renal dialysis.

Apstrakt

Uvod/Cilj. Inflamacija je jedan od najčešćih faktora koji doprinose rezistenciji na terapiju agensima koji stimulišu eritropoezu (ASE) kod bolesnika na hemodijalizi. U novije vreme se procenjuje korišćenje novih markera upale, a to su odnos trombocita i limfocita (TLO) i odnos neutrofila i limfocita (NLO). Njihova povezanost sa terapijom eritropoetinom nije u potpunosti istražena. Cilj rada bio je da se proceni povezanost između TLO, NLO i ASE indeksa hiporesponsivnosti (AIHR). **Metode.** Istraživanje je sprovedeno kao studija preseka i obuhvatila je 90 bolesnika na hemodijalizi, kojima je urađeno kliničko i laboratorijsko ispitivanje u vidu fizikalnog pregleda i biohemijskih analiza. Kod svih bolesnika izračunat je AIHR. **Rezultati.** Utvrđeno je da je AIHR imao statistički značajnu pozitivnu korelaciju sa TLO ($p < 0,01$) i negativnu korelaciju sa nivoima hemoglobina ($p < 0,01$). Pronađene su značajne razlike za logaritamski konvertovane vrednosti AIHR i TLO ($p < 0,05$), ali ne i za IHRE i NLO ($p = 0,13$). **Zaključak.** Istraživanje je pokazalo da bi se TLO, zajedno sa NLO, mogao koristiti za procenu ne samo inflamacije, već i rezistencije na terapiju eritropoetinom kod bolesnika na hemodijalizi.

Ključne reči:
trombociti; eritropoetin; zapaljenje; limfociti; neutrofili; hemodijaliza.

Introduction

End-stage renal disease (ESRD) is characterized by many accompanying complications, out of which anemia is the most common and is associated with an increased risk of hospitalization and death. Inflammation is one of the key factors that contribute to erythropoiesis stimulating agents (ESA) hyporesponsiveness, and it is associated with increased activation of neutrophils and platelets (PLT). PLT-to-lymphocyte ratio (PLR) has been identified as a possible

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predictor of ESA hyporesponsiveness index (EHRI) and inflammation in ESRD [1].

It is unclear whether neutrophil-to-lymphocyte ratio (NLR) and/or PLR, which have been identified as markers of increased inflammation in ESRD patients, could have a relationship and clinical utility in assessing response to ESA and EHRI.

Almost 90% of all ESRD patients have anemia, and thus a diminished quality of life, and are at an increased risk of developing cardiovascular problems, leading to frequent hospitalization [2, 3].

Many causes of anemia in ESRD, such as inadequate dialysis, hyperparathyroidism, iron deficiency, occult blood loss, vitamin B12 deficiency, folate deficiency, have already been identified; however, the greatest contributor to anemia is the relative deficiency of erythropoietin (EPO) secretion from the affected kidney that is in correlation with the degree of anemia [4]. With the development and advent of ESA, a significant improvement in the treatment of anemia and its side effects has been achieved, resulting in a reduced need for blood transfusions and a lower mortality rate. Therefore, ESA therapy is nowadays the gold standard for the treatment of anemia in chronic kidney disease [5]. Even with this therapeutic approach, some patients have a reduced response to ESA therapy, which is defined as ESA hyporesponsiveness, with half (50%) of them being intermittent hyporesponders [6]. ESA hyporesponsiveness is defined as a failure to achieve the recommended target HGB levels despite a higher than usual dose of ESA or a continuous need for high doses to maintain the target HGB levels [7]. A meta-analysis conducted by Wish [6] describes ESA hyporesponsiveness as the failure to achieve the target HGB concentration of > 11 g/dL in patients who receive ESA dose equivalent to more than 500 IU/kg EPO per week or who have a prolonged need for such high dosages to maintain the target. Since HGB levels were not included by the aforementioned author, EHRI has been established and calculated as the weekly dose of ESA *per* kilogram of body weight divided by the HGB level (g/dL), making it extremely useful and easy to assess EPO resistance [8, 9].

One study has clearly identified many factors which have an impact on ESA responsiveness, among which inflammation, malnutrition, iron deficiency, secondary hyperparathyroidism, and inadequate dialysis are the most common and contribute to higher morbidity and mortality rates [10]. Furthermore, it is now widely known that patients with ESA hyporesponsiveness have increased inflammatory markers, which only indicates that inflammation is one of the main factors influencing the overall response [1].

In everyday common practice, many diagnostic and monitoring inflammatory markers are being used; however, new biological markers of inflammation are emerging. PLR and NLR have begun to be used not only in assessing cardiovascular risk and mortality but also in kidney patients and are tightly linked to inflammation and endothelial damage [1, 11]. Leukocyte count is strongly associated with increased cardiovascular mortality, and some studies find that certain subsets of leukocytes have even higher predictive value in the overall mortality, inflammation, and tissue damage than total white blood count. When NLR is used, such risk is even higher [12, 13].

In hemodialysis and peritoneal dialysis patients, NLR and PLR are associated with increased inflammation, whereas in the last couple of years, PLR was found to be associated with inflammation even more than NLR in these patients [11].

Taking into consideration the data mentioned above, the aim of the study was to identify NLR and/or PLR as markers of increased inflammation in ESRD patients and its relation and clinical utility in assessing ESA responsiveness and EHRI.

Methods

Study design and ethics statement

The study design was cross-sectional and it was approved by the Ethics Committee of the Faculty of Medicine, University of Novi Sad (No. 01-39/28/1, from April 18, 2018). Written informed consent was obtained from all patients before enrollment. Inclusion criteria for enrollment in the study were the following: clinically stable patients older than 18 years of age, undergoing hemodialysis at the Dialysis Unit of Clinic for Nephrology and Clinical Immunology, University Clinical Center of Vojvodina, Serbia for at least six months, and receiving ESA treatment.

Study population and data collection

The study initially included 118 patients undergoing regular hemodialysis at our Unit. Those patients with a history of iron deficiency (serum ferritin values < 30 ng/mL), current infection, hematologic disorders and malignancies, history of blood transfusions and hospital admission in the last three months, or undergoing steroid treatment were excluded from the study, including patients with elevated C-reactive protein (CRP) levels in order to evaluate the relationship between EHRI, NLR, and PLR exclusively. In total, 28 patients were excluded from the study. After a thorough evaluation, 18 patients were excluded from the study. They had at least one of the exclusion criteria, i.e., mostly active infection, hematologic malignancies, and a history of recent blood transfusions. Ten patients did not receive ESA therapy due to satisfactory HGB levels (thus, no correction was required according to the guidelines; HGB level above 110 g/L) [6]. Demographic characteristics such as age, gender, body mass index (BMI), fat and lean tissue index, smoking status, dietary habits, etiology of ESRD, and medical history were recorded. In all patients, the dialysis prescription was three times a week for 4–5 hrs with blood flow rates of 300–400 mL/min, using a standard bicarbonate solution. A clinical examination was performed, with an emphasis on BMI and blood pressure. We collected three consecutive monthly laboratory records, which included blood count, renal function tests (blood urea, creatinine), data on mineral bone disease (calcium, phosphorus, intact parathormone), serum albumin, iron status (iron, transferrin, ferritin), and lipid status parameters (total cholesterol, triglycerides). The EHRI was calculated as the weekly ESA dose *per* kilogram of body weight divided by the HGB level (g/L). The mean HGB level

and EPO dose *per* month during three months were used for this calculation. The calculation of NLR was done by dividing the absolute neutrophil count (ANC) by the absolute lymphocyte count (ALC), whereas PLR was calculated by dividing the absolute PLT count by the ALC. Mean reference values and corresponding 95% reference intervals for the inflammatory markers, according to the study conducted on 8,711 healthy participants, for the NLR were 1.76 (0.83–3.92), and for PLR 120 (61–239) [14]. A study performed by Rabea et al. [7] showed that patients on hemodialysis who show signs of ESA hyporesponsiveness measured by EHRI have higher levels of PLR, with a median of 119.2 as opposed to patients in the group of good responsiveness who have lower levels of PLR with a median of 95.8.

Statistical analysis

The SPSS 20.0 software package was used for data processing (SPSS, Evanston, IL, USA). Descriptive statistics methods were used to measure central tendency (arithmetic mean, median) and measures of variability (standard deviation) in order to summarize the major numerical characteristics of observations. Data were checked for normality. The normality of the variables was analyzed using the Shapiro-Wilk test, which did not find evidence of a lack of normality in the residuals ($p = 0.20$). The Pearson coefficient was used for correlations. For the comparison of PLR among EHRI percentiles, the Kruskal-Wallis test was used. In the applied analyses, statistically significant differences were at the significance level of 95% ($p < 0.05$).

Results

Patient characteristics

The study was conducted on 90 patients undergoing maintenance dialysis and receiving ESA therapy. The median age of patients was 60.45 [± standard deviation (SD) 11.58] years, and, in total, 33 (36.7%) patients received darbepoetin alfa, whereas the remaining 57 patients received other short-acting ESA agents. The average HGB value in our sample was 105.79 (± SD 12.44) g/L, whereas the median applied dose of darbepoetin alfa *per* kilogram of body weight was 0.22 (± SD 0.14) mcg/kg and of short-acting ESA was 50.11 (± SD 28.11) IU/kg. In this study, we did not include patients with CRP levels to assess the relationship between NLR, PLR, and EHRI exclusively. Other descriptive data, demographic, clinical, and laboratory values are presented in Table 1.

Characteristics of EHRI and correlated novel markers of inflammation

In order to assess the correlation between EHRI and the other observed parameters, the Pearson correlation coefficient was used. In Table 2, EHRI values in all three meas-

Table 1

Descriptive data of the sample

Parameter	Reference range	N	Values
Age (years)		90	60.45 ± 11.58
EHRI[#]		81	4.98 (0.73–11.34)
Erythrocytes ($\times 10^{12}$/L)	3.9–5.4	90	3.43 ± 0.43
Hemoglobin (g/L)	120–160	81	105.79 ± 12.44
Hematocrit (%)	0.4–0.5	90	0.33 ± 0.037
CRP* (mg/dL)	0–5	87	5.20 (0.1–25.20)
Albumin (g/L)	35–52	87	36.93 ± 3.16
Ferritin (μg/L)	10–120	87	661.13 ± 484.39
Saturation transferrin (%)	15–50	87	30.12 ± 17.20

EHRI – ESA hyporesponsiveness index; ESA – erythropoiesis stimulating agents; CRP – C-reactive protein; NLR – neutrophil-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio; N – number of patients.
All values are expressed as mean ± standard deviation except EHRI and CRP, which are expressed as mean (minimum–maximum).
Note: #EHRI was calculated by dividing weekly ESA dose per kilogram of body weight (IU/kg/week) by hemoglobin level (g/dL); *Three patients were not included in the study due to elevated CRP levels, in order to assess the relationship between NLR, PLR, and EHRI exclusively.

Table 2

Correlation between log EHRI and different independent variables measured in each of the three months

Parameter	Erythropoietin resistance		
	1st month	2nd month	3rd month
NLR	0.13	0.15	0.19
PLR	0.28**	0.30**	0.49**
HGB	-0.49**	-0.57**	-0.40**

EHRI – ESA hyporesponsiveness index; NLR – neutrophil-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio; HGB – hemoglobin.
****$p < 0.01$.**

urements are presented. It is shown that EHRI had a statistically significant correlation with PLR of low to medium intensity (r_1 = 0.28, p < 0.01; r_2 = 0.30, p < 0.01; r_3 = 0.49, p < 0.01). There was a negative correlation of medium degree between EHRI and HGB levels (r_1 = -0.49, p < 0.01; r_2 = -0.57, p < 0.01; r_3 = -0.40, p < 0.01).

The correlation between NLR and PLR in all three measurements is shown in Table 3.

The relationship between the NLR, PLR, and the logarithmically converted levels of EHRI was examined firstly by using the Kruskal-Wallis test, which showed statistically significant differences for EHRI and PLR (p < 0.05) but not for EHRI and NLR (p = 0.13) in any of the three measurements. Significant differences in the distribution of EHRI for the different EHRI percentiles (p < 0.05) are presented in Figure 1. PLR from the first measurement (Figure 1A) was in correlation with logarithmically converted EHRI from the same measurement (p < 0.01). The Tukey multiple comparison tests were used to determine among which percentiles the PLR differences were found. *Post hoc* analysis indicated a statistically significant correlation between EHRI and PLR up to the 50th percentile (p < 0.05), while above the 50th percentile, there is no statistically significant correlation between EHRI and PLR. In the second measurement (Figure 1B), EHRI was associated with logarithmically converted EHRI (p < 0.01). *Post hoc* analysis revealed a statistically significant correlation between the 25th and 50th percentile (< 0.05) as well as for the 50th and 75th percentile (p < 0.05). PLR from the third measurement (Figure 1C) was associated with logarithmically converted EHRI from the third measurement (p < 0.01). Examination of *post hoc* analysis showed a significant correlation for the first (p < 0.05) and the second half of the curve (p < 0.01), bearing in mind that there was a stronger correlation between EHRI and PLR above the 50th percentile.

Discussion

In this study, we aimed to identify the correlation between EPO resistance and novel markers of inflammation NLR and PLR. To assess the response to EPO treatment, we used a body weight-adjusted dose of EPO and HGB levels as it is predefined by the EHRI equation. From the obtained results, we managed to demonstrate that PLR was independently associated with EHRI as opposed to NLR and EHRI. The results are consistent in all three measurements. These results are in agreement with other studies, while a possible explanation for these findings might lay in the fact that PLR is a better inflammatory marker than NLR [15–18]. Chávez et al. [19] found that the correlation between PLR and inflammatory parameters was superior to that obtained by NLR. Opposite to our research, Valga et al. [18] found a significant association of the EHRI with both parameters, whereas low lymphocyte levels were given as a possible explanation for this finding.

Many factors have already been independently associated with ESA resistance; however, inflammation is still the leading cause of this condition [19]. Chronic inflammation, identified most commonly by elevated levels of CRP, interleukin (IL)-6, and tumor necrosis factor (TNF)-alpha, presents a part of malnutrition-inflammation-atherosclerosis syndrome in patients with ESRD [19–22]. Novel inflammation markers PLR and NLR have been found to be in positive correlation with IL-6 and TNF-α so much that PLR was better than NLR at predicting inflammation [16]. Okyay et al. [23] demonstrated a strong positive correlation between NLR and inflammatory cytokines such as IL-6 and CRP.

PLT have a wide range of interactions with different cell subsets, and there is emerging evidence that they can influence leukocyte recruitment, causing inflammation, which is the pathogenic mechanism of atherosclerosis, making them an important factor in this process by actively secreting pro-

Table 3

Correlation between NLR and PLR in all three measurements

Parameter	NLR		
	r_1	r_2	r_3
NLR	-	-	-
PLR	0.63**	0.71**	0.53**

For abbreviations see Table 2. **p < 0.01.

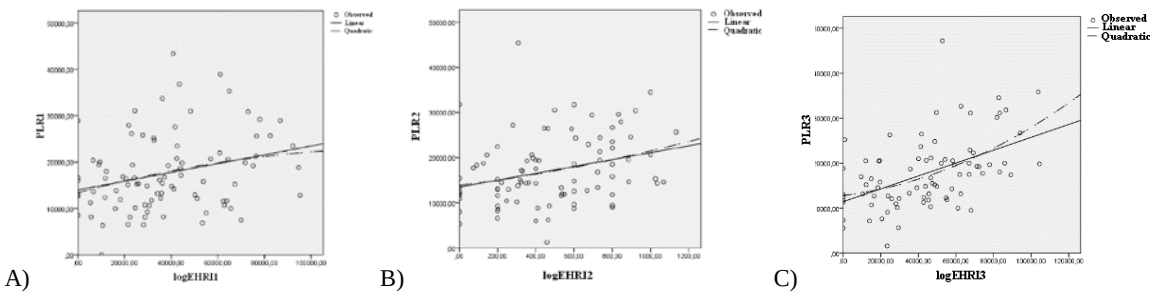

Fig. 1 – Correlation between PLR and logarithmically converted EHRI in three measurements. For abbreviations see Table 2.

inflammatory cytokines [23–26]. The advantage of the PLR is that it shows both hyperactive coagulation and inflammatory pathways, making it superior to the individual PLT or lymphocyte counts in the prediction of inflammation and consequential EPO resistance [26].

In our research, 10% of patients had HGB levels over 110 g/L; therefore, in accordance with international guidelines, no EPO treatment was administered [7]. In the remaining patients, HGB levels were corrected by an individually adjusted ESA dosing regimen. In this research, we have found a statistically significant negative correlation between the HGB levels and therapeutic response to ESA represented by EHRI, which indicates that less stable levels of HGB have a negative impact on ESA treatment response.

The obtained results show a positive association between NLR and PLR, which indicates that in inflammatory conditions, there is simultaneous activation of these blood cells, and they might be considered predictors of ESA resistance in ESRD patients. In patients undergoing maintenance dialysis with an ongoing inflammatory process, PLR and NLR are elevated [18, 26]. Meanwhile, inflammation in hemodialysis patients is a risk factor contributing to higher morbidity and mortality rates [9]. Additionally, a statistically significant difference was found between groups of patients with resistance to EPO and PLR once divided into percentile ranges. The data obtained from our research only confirms previous findings that show that PLR could be a good marker of EHRI and possibly inflammation in the population of patients with stage V of chronic kidney disease [10].

Conclusion

By being both financial and time-consuming, PLR and NLR are universally accessible methods and could be used in screening and evaluation of inflammation in ESRD patients, thereby assessing ESA response. Simple calculations of PLR are superior to NLR in predicting ESA response in these patients. We firmly believe that these markers, especially PLR, can be routinely used in everyday dialysis practice as markers of not only mortality but also inflammation and therapeutic response. However, additional randomized and controlled studies are imperative to assess PLR, NLR, and EHRI in ESRD patients.

REFERENCES

1. *Valga F, Monzón T, Henriquez F, Antón-Pérez G.* Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as biological markers of interest in kidney disease. Índices neutrófilo-linfocito y plaqueta-linfocito como marcadores biológicos de interés en la enfermedad renal. Nefrologia (Engl Ed) 2019; 39(3): 243–9.
2. *El Sewefy DA, Farweez BA, Behairy MA, Yassin NR.* Impact of serum hepcidin and inflammatory markers on resistance to erythropoiesis-stimulating therapy in haemodialysis patients. Int Urol Nephrol 2019; 51(2): 325–34.
3. *Chen L, Ling YS, Lin CH, He JX, Guan TJ.* High Dose ESAs Are Associated with High iPTH Levels in Hemodialysis Patients with End-Stage Kidney Disease: A Retrospective Analysis. Front Public Health 2015; 3: 258.
4. *Afsar B.* The relationship between depressive symptoms and erythropoietin resistance in stable hemodialysis patients with adequate iron stores. Int J Artif Organs 2013; 36(5): 314–9.
5. *Afsar B, Saglam M, Yuceturk C, Agca E.* The relationship between red cell distribution width with erythropoietin resistance in iron replete hemodialysis patients. Eur J Intern Med 2013; 24(3): e25–9.
6. *Wish JB.* Erythropoiesis-Stimulating Agent Hyporesponsiveness and Adverse Outcomes: Guilty as Charged? Kidney Med 2020; 2(5): 526–8.
7. *Rabea A, Ragheb A, Emara M, Kamal AM.* Predictors of erythropoietin hyporesponsiveness in chronic hemodialysis patients. Menoufia Med J 2020; 33(1): 105–9.
8. *López-Gómez JM, Portolés JM, Aljama P.* Factors that condition the response to erythropoietin in patients on hemodialysis and their relation to mortality. Kidney Int Suppl 2008; (111): S75–S81.
9. *López-Gómez JM, Pérez-Flores I, Jofré R, Carretero D, Rodriguez-Benitez P, Villaverde M*, et al. Presence of a failed kidney transplant in patients who are on hemodialysis is associated with chronic inflammatory state and erythropoietin resistance. J Am Soc Nephrol 2004; 15(9): 2494–501.
10. *Ogawa T, Shimizu H, Kyono A, Sato M, Yamashita T, Otsuka K*, et al. Relationship between responsiveness to erythropoiesis-stimulating agent and long-term outcomes in chronic hemodialysis patients: a single-center cohort study. Int Urol Nephrol 2014; 46(1): 151–9.
11. *Turkmen K, Erdur FM, Ozcicek F, Ozcicek A, Murat Akbas E, Ozbicer A,* et al. Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in end-stage renal disease patients. Hemodial Int 2013; 17(3): 391–6.
12. *Kim WH, Park JY, Ok SH, Shin IW, Sohn JT.* Association Between the Neutrophil/Lymphocyte Ratio and Acute Kidney Injury After Cardiovascular Surgery: A Retrospective Observational Study. Medicine (Baltimore) 2015; 94(43): e1867.
13. *Afsar B.* The relationship between neutrophil lymphocyte ratio with urinary protein and albumin excretion in newly diagnosed patients with type 2 diabetes. Am J Med Sci 2014; 347(3): 217–20.
14. *Fest J, Ruiter R, Ikram MA, Voortman T, van Eijck CHJ, Stricker BH,* et al. Reference values for white blood-cell-based inflammatory markers in the Rotterdam Study: a population-based prospective cohort study. Sci Rep 2018; 8(1): 10566.
15. *Horne BD, Anderson JL, John JM, Weaver A, Bair TL, Jensen KR*, et al. Which white blood cell subtypes predict increased cardiovascular risk? J Am Coll Cardiol 2005; 45(10): 1638–43.
16. *Taymez DG, Ucar E, Turkmen K, Ucar R, Afsar B, Gaipov A*, et al. The Predictive Value of Platelet/Lymphocyte Ratio in Hemodialysis Patients With Erythropoietin Resistance. Ther Apher Dial 2016; 20(2): 118–21.
17. *Turkmen K, Erdur FM, Ozcicek F, Ozcicek A, Akbas EM, Ozbicer A*, et al. Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in end-stage renal disease patients. Hemodial Int 2013; 17(3): 391–6.
18. *Valga F, Monzón T, Henriquez F, Santana-Del-Pino A, Antón-Pérez G.* Platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios as markers of erythropoietin resistance in chronic haemodialysis patients: a multicentre cross-sectional study. Nefrologia (Engl Ed) 2020; 40(3): 320–7. (English, Spanish)
19. *Chávez Valencia V, Orizaga de la Cruz C, Mejía Rodríguez O, Gutiérrez Castellanos S, Lagunas Rangel FA, Viveros Sandoval ME.* Inflammation in hemodialysis and their correlation with neutrophil-lymphocyte ratio and platelet- lymphocyte ratio. Nefrologia 2017; 37(5): 554–6. (English, Spanish)

20. *Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C.* Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int 1999; 55(2): 648–58.
21. *Iseki K, Tozawa M, Yoshi S, Fukiyama K.* Serum C-reactive protein (CRP) and risk of death in chronic dialysis patients. Nephrol Dial Transplant 1999; 14(8): 1956–60.
22. *Yeun JY, Levine RA, Mantadilok V, Kaysen GA.* C-Reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. Am J Kidney Dis 2000; 35(3): 469–76.
23. *Okyay GU, Inal S, Oneç K, Er RE, Pasaoglu H, Derici U,* et al. Neutrophil to lymphocyte ratio in evaluation of inflammation in patients with chronic kidney disease. Ren Fail 2013; 35(1): 29–36.
24. *Langer HF, Gawaz M.* Platelet-vessel wall interactions in atherosclerotic disease. Thromb Haemost 2008; 99(3): 480–6.
25. *Kaplan ZS, Jackson SP.* The role of platelets in atherothrombosis. Hematology Am Soc Hematol Educ Program 2011; 2011: 51–61.
26. *Huo Y, Ley KF.* Role of platelets in the development of atherosclerosis. Trends Cardiovasc Med 2004; 14(1): 18–22.

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