Platelet-To-Lymphocyte Ratio and Arteriovenous Fistula for Hemodialysis: An Early Marker to Identify AVF Dysfunction

Articoli originali

Roberta Maria Messina[1], Vincenzo Calabrese[2], Fortunata Zirino[1], Antonella Lipari[1], Alfio Edoardo Giuffrida[1], Concetto Sessa[1], Dario Galeano[1], Ivana Alessandrello[1], Giulio Distefano[1], Viviana Scollo[1], Carmelo Zuppardo[1], Domenico Santoro[2], Walter Morale[1]

1 Department of Nephrology and Dialysis "Maggiore" Hospital Modica, Ragusa, 97015, Italy
2 Department of Clinical and Experimental Medicine, Unit of Nephrology and Dialysis, A.O.U. "G. Martino", University of Messina, Messina, 98125, Italy

Corresponding author:
Roberta Maria Messina
Tel: +39 34076769584
E-mail: robertamaria.messina@asp.rg.it


Roberta Maria Messina

ABSTRACT

The KDOQI guidelines (*Kidney Disease Outcomes Quality Initiative*) recommend autologous arteriovenous fistula (AVF) as the primary vascular access in hemodialysis patients because of the higher quality of life and lower complication rates if compared to arteriovenous grafts (AVGs) or central venous catheter (CVC). Several studies used various inflammatory biomarkers to evaluate the association between systemic inflammation and AVF dysfunction. A novel inflammatory biomarker, the platelet–lymphocyte ratio (PLR), is a useful and easy laboratory parameter that can reveal systemic inflammation. Our study aimed to evaluate the relationship between PLR value changes over time and AVF dysfunction. The impact of PLR on our outcome showed a trend close to the significance (OR: 4,9; 95%CI: [0.84-28.5]; p = 0.08) but the *slope* was not linear. Therefore, we performed the same analysis splitting the patients by the median PLR value and we highlighted a significant relationship between our outcome and the PLR (log-transformed) for PLR-value under the median value (OR: 9.97; 95%CI: [2.53-39.25]; p = 0.001). Furthermore, in patients with PLR above the median value, the interaction visit-PLR showed an impact close to the statistical significance (OR: 7.7; 95%CI: [0.81-72.97]; p = 0.07). PLR (log-transformed) was positively correlated with AVF age (Rho: 0.254, p = 0.002).

KEYWORDS AVF, chronic kidney disease, hemodialysis, platelet-lymphocite ratio, thrombosis

Introduction

The KDOQI guidelines (*Kidney Disease Outcomes Quality Initiative*) recommend autologous arteriovenous fistula (AVF) as the primary vascular access in hemodialysis patients because of the higher quality of life and lower complication rates if compared to arteriovenous grafts (AVGs) or central venous catheter (CVC) [1–3]. Several studies evaluated the association between systemic inflammation and AVF dysfunction using various inflammatory biomarkers [4, 5, 10].

A novel inflammatory biomarker, the platelet-lymphocyte ratio (PLR), is a useful and easy laboratory parameter that can reveal systemic inflammation [1]. Various studies showed how the PLR values are linked to chronic inflammation in different clinical conditions [8, 12]. Our study aimed to evaluate the relationship between PLR value changes over time and AVF dysfunction (both stenotic and/or thrombotic complications) in our group of patients undergoing chronic hemodialysis (HD) at our center.

Material and Methods

We, at first, evaluated 53 patients in chronic HD related to our center. Inclusion criteria were the following: start of HD therapy for at least one month, AVF (or AVGs) as the vascular access for HD, and patients over 18 years of age. Exclusion criteria were an active infectious disease, malignancy, chronic corticosteroid therapy, hematological diseases, a recent history of major bleeding, and patients with central venous catheters. Out of the initial pool of candidates, 12 patients were excluded following the criteria described above (5 patients had a central venous catheter, 2 patients had an autoimmune thrombocytopenia, 3 patients had a diagnosis of monoclonal gammopathy, 1 patient had tumoral disease and 1 of them had an active infectious disease).

Statistical Analysis

For all patients, we performed four visits (from March 2022 to June 2022) evaluating: hemoglobin value, platelet count, lymphocyte absolute count, reactive C protein (RCP), PLR, calcium, phosphate, calcium/phosphorus product, cholesterol, LDL, HDL (tested before the start of HD session), the timing of HD therapy, elderly of AVF and type (distal AVF, proximal AVF or AVG), underlying pathology, comorbidities (history of cardiovascular disease, hypertension and/or diabetes mellitus).

All patients included in the study underwent anticoagulant therapy during the HD session using heparin (in 32 patients continuous administration was performed, 5000 IU at the rate, on average, of 3 ml\h and 3 ml\bolus; the administration was interrupted at 30-45 minutes to the end of the session); 2 patients underwent to anticoagulant therapy using fondaparinux (1.5mg/0.3ml).

At the beginning of the study, we also performed an ECD (eco-color-doppler) examination to evaluate the AVF blood flow. AVF blood flow was measured by a linear probe (5-11MHz) along the axis of the brachial artery above the elbow fold. Flow rate value expressed in mL/min. During each visit, we evaluated: platelet count in absolute number, absolute lymphocyte count, PLR, neutrophils (%), hemoglobin value, triglycerides, HDL, C-reactive protein (CRP), calcium/phosphorus product, first-hour erythrocyte sedimentation rate (ESR).

The categorical variables (gender, drug therapy, and comorbidities) were expressed as number and percentage; the numerical variables (age, age of AVF, etc.) were expressed as mean ± standard deviation (SD) and median [interquartile range]. The Kolmogorov-Smirnov test was first applied to verify the normality of the distribution of the examined variables. Spearman and Pearson correlation

tests were used to investigate the existence of relationships of interdependence between variables. Cox regression analysis was performed to calculate the hazard ratio (person-time incidence) of vascular access complications (stenosis, thrombosis, and/or bleeding). Cox regression was performed both in the entire sample and in the two sub-samples divided by the median PLR value. The "PLR" variable was log-transformed to make its distribution normal. The statistical significance level is 0.05 for all the endpoints included. The statistical software used is SPSS for Windows version 24.0 and STATA version 13.

Results

A total of 41 patients (37% female, 63% male) were enrolled in our analysis; 92% were affected by hypertension, 24% were affected by diabetes and 24% had a history of cardiovascular disease. The average age of the patients included in the study was 67±16 years. The median PLR was 192 [IQR:138-256]; the value of PLR was log-transformed based on its distribution. The median age was 68 [IQR: 55-81] years and the median AVF age was 3 [IQR: 1.8-4.3] years. Baseline hemoglobin was 10.8 g/dl [IQR: 9.5-11.7], platelet where 242.000±89000, serum ferritin was 168 [72-618], VES at the first hour was 44 [30-75] and CRP was 0.45 mg/dl [0.12-0.85]. Neutrophils were 72.2% ± 6.7%; Calcium was 8.7 mg/dL [IQR 8,3-9,1], phosphate was 4.8 mg/dL [IQR: 4-5.9] (Table 1). 3 out of 41 patients had brachial-basilic fistula, 1 had a proximal AVG; the remaining had a distal AVF. 90.2% of the patients included in the study had a distal AVF (radio-cephalic), 7.3% had a proximal AVF, and 2.43% had an AVG (Table 2).

Hb g/dL	10.8 g/dL	[IQR 9.5-11.7]
VES 1^hr	44	[IQR 30-75]
CRP mg/dL	0.45 mg/dL	[IQR 0.12-0.75]
Platelet	242.000	242.000-89.000
PLR	192	[IQR 138-256]
Neutrophils	72.2%	± 6.7
Calcium mg/dL	8.7 mg/dL	[IQR 8.3-9.1]
Phosphate mg/dL	4.8 mg/dL	[IQR 4-5.9]

Table 1. Laboratory data.

Type of vascular access	%	Blood Flow
Distal AVF	90%	986 ± 400 ml/min
Proximal AVF	7.55%	1556 ml/min
AVG	2.45	1470 ml/min 1370 ml/min 1265 ml/min

Median age of AVF/AVG	3yr	[IQR 1.8-4,3]

Table 2. AVF/AVGs blood flow and median age.

During the observational period, we recorded AVF complications (both stenotic and thrombotic) in 11 patients:

- Patient 1: cephalic vein stenosis on radio-cephalic AVF treated with transluminal angioplasty (PTA). Axillary vein stenosis coexisted up to the confluence in the subclavian vein.
- Patient 2: peri-anastomotic stenosis treated with PTA on mid-arm AVF.
- Patient 3: left radio cephalic AVF with aneurysm thrombosis treated with the creation of a new brachiomedian AVF.

- Patient 4: cephalic vein stenosis on brachiocephalic AVF treated with the creation of AVG (arteriosus-venous graft).
- Patient 5: brachiobasilic AVF stenosis treated with PTA.
- Patient 6: juxta-anastomotic stenosis on radio-cephalic AVF treated with PTA.
- Patient 7: cephalic vein stenosis on left radio cephalic AVF treated with PTA.
- Patient 8: cephalic vein stenosis on right radio cephalic AVF treated with PTA.
- Patient 9: juxta-anastomotic stenosis on left radio-cephalic AVF treated with PTA.
- Patient 10: thromboembolectomy + stenting basilic vein on proximal AVF.
- Patient 11: cephalic vein stenosis on brachiocephalic AVF treated with the creation of AVG on the same side.

The impact of PLR on our outcome was not statistically significant, but it shows a trend close to the significance (OR: 4.9; 95%CI: [0.84-28.5]; p = 0.08) but the *slope* was not linear (Figure 1).

Therefore, we performed the same analysis splitting the patients by the median PLR value and we highlighted a significant relationship between our outcome and the PLR (log-transformed) for PLR-value under the median value (OR: 9.97; 95%CI: [2.53-39.25]; p = 0.001) (Table 3).

Furthermore, in patients with higher PLR (above the median value), the interaction visit-PLR showed an impact close to the statistical significance (OR: 7.7; 95%CI: [0.81-72.97]; p = 0.07) (Table 4). PLR (log-transformed) was positively correlated with AVF age (Rho: 0.254, p = 0.002).

Our study has some limitations: the number of patients enrolled is certainly exiguous, and in the short observation period (March-June 2022) we highlighted just 11 events. Nevertheless, it is interesting to see how the values of PLR, in our population, were associated with the incidence of AVF's complications.

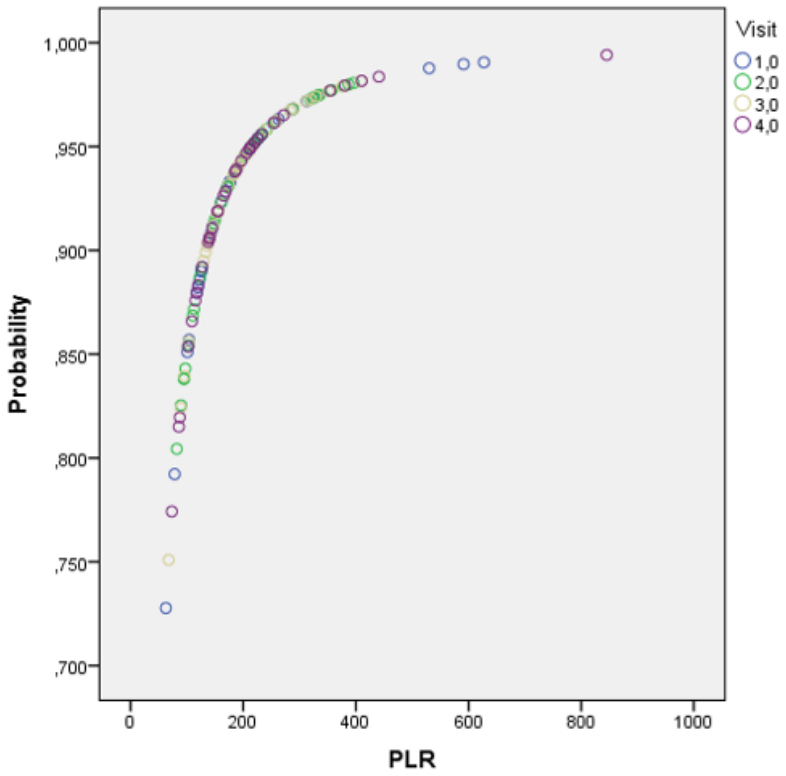

Figure 1. The impact of PLR on our outcome.

	PLR lower than median		PLR upper than median	
	OR	p	OR	p
PLR (ln)	9.97	0.0001	0.06	0.11

Table 3. Univariate impact of PLR (log-transformed) on thrombosis for PLR median.

	PLR lower than median		PLR upper than median	
	OR	p	OR	p
PLR (ln)	2.91	0.67	0.001	0.06
Visit	0.10	0.65	0.0001	0.07
Interaction	1.72	0.62	7.70	0.07

Table 4. Univariate impact of interaction between PLR (log-transformed) and time on thrombosis split for median PLR.

Discussion

This study aimed to identify the presence of possible interaction and correlation between PLR values and the onset of access-related complications of vascular disease in patients undergoing periodic hemodialysis therapy at our facility Center. As previously described the PLR has recently been used as a marker of systemic inflammation during inflammatory and/or tumor pathologies [13, 15]; its increase has also been associated with pathologies related to thrombotic risk such as, for example, acute coronary disease [16].

There is not much data in the literature regarding the correlation between PLR and the onset of complications (in terms of stenosis or thrombosis) of arteriovenous fistulas for hemodialysis. A 2019 study [17] highlighted how PLR presented significantly higher values in patients with stenosis and/or thrombosis hypothesizing therefore the role of PLR as a marker of AVF dysfunction. A second study from 2021 [18] examined patients with hemodynamically significant stenosis (reduction of more than 50% in vessel caliber) treated with angioplasty highlighting an increased PLR value at the time of the procedure, which could represent a risk factor for the development of early restenosis after PTA. A recent study, published in September 2022, evaluated the possible predictive role of PLR and NLR (neutrophil-to-lymphocyte ratio) against the onset of early malfunction of native AVFs, highlighting how both markers could be useful in risk stratification of complications related to vascular access in patients undergoing hemodialysis. Furthermore, the NLR value was identified as an independent risk factor for AVF failure [19]. In 2024 Franchin et al. evaluated the predictive value of NLR, PLR and SII (systemic-immune-inflammation index) in the onset of AVG stenosis. The authors highlighted how higher value of NLR and SII related to stenosis onset and recurrence; contrariwise, they do not find statistical differences between AVG stenosis and PLR values [20].

Our analysis shows the role of PLR in predicting the onset of stenotic and/or thrombotic complications in patients with AVF for hemodialysis. Analyzing the median values of the PLR we highlighted how the values below the median value had a statistically significant association with our outcome and therefore with the onset of access complications vascular for hemodialysis. Above the median values, however, we obtained values tending towards significance. This demonstrates how PLR values gradually higher and their increase over time could represent a useful marker to monitor vascular access health.

Values progressively elevated could (along with the physical examination, the data of dialysis efficiency, and the ECD) direct the clinician to perform an imaging test to achieve an early identification of stenosis and/or thrombosis leading to early treatment of these conditions through

procedures such as PTA and/or surgical revision allowing the "*saving*" of vascular access, preserving the patient's vascular heritage, and reducing the use of venous central catheters as definitive access.

Limitations

The number of patients enrolled is certainly limited, and in the short observation period (March-June 2022) we only highlighted 11 events. Another limitation of our study is the homogenous kind of vascular access found in our patients. We enrolled 41 patients, and, of these, 37 patients (90.2%) had a distal AVF (radio-cephalic); 7 of these patients had stenotic complications during the observational period vs 4 events seen in patients with a proximal AVF. Definitely, more studies are needed; it can be useful to evaluate the value of PLR correlation with stenotic and/or thrombotic complications in a different and large cohort. Despite this, it is interesting to see how the values of PLR, in our population, are associated with the incidence of complications stenotic, thrombotic, and, in general, the onset of complications required angioplasty interventions to ensure the patency of the AVF or, following the loss of vascular access, surgical revision with the creation of new vascular access of the AVF through the use of native vessels or with the use of prosthetic material.

Conclusion

The evaluation of PLR is extremely easy and it makes the PLR value a possible parameter that can be used in parallel with the clinical examination and ECD study in all contexts, not just Hospitals, given the almost zero cost and simplicity of execution. The aim of the study, as previously mentioned, is to find the possible correlation between PLR and stenotic/thrombotic complications of AVFs for hemodialysis. The ultimate attempt is to identify a further useful parameter in the prevention of complications associated with vascular access with the aim of preserving it as much as possible, guaranteeing a safe and effective vascular access for patients undergoing hemodialysis therapy, minimizing the risk of local and systemic complications, reducing the number of hospitalizations and, above all, helping to preserve the central and peripheral vascular heritage of the patient.

G Ital Nefrol 2024 - ISSN 1724-5990 - © 2024 Società Italiana di Nefrologia - Anno 41 Volume 6 – DOI: 10.69097/41-06-2024-12

BIBLIOGRAPHY

1. Perico N and Remuzzi G. Chronic kidney disease: a research and public health priority. *Nephrol Dial Transplant* 2012; 27 (Suppl. 3): iii19–iii26. https://doi.org/10.1093/ndt/gfs284.
2. NKF-K/DOQI Clinical practice guidelines for vascular access: update 2000. *Am J Kidney Dis* 2001; 37(1, Suppl. 1): S137–S181. https://doi.org/10.1016/s0272-6386(01)70007-8.
3. Polkinghorne KR, McDonald SP, Atkins RC, et al. Vascular access and all-cause mortality: a propensity score analysis. *J Am Soc Nephrol* 2004; 15(2): 477–486. https://doi.org/10.1097/01.asn.0000109668.05157.05.
4. Marrone D, Pertosa G, Simone S, et al. Local activation of interleukin 6 signaling is associated with arteriovenous fistula stenosis in hemodialysis patients. *Am J Kidney Dis* 2007; 49(5): 664–673. https://doi.org/10.1053/j.ajkd.2007.02.266.
5. Roy-Chaudhury P, Khan R, Campos B, et al. Pathogenetic role for early focal macrophage infiltration in a pig model of arteriovenous fistula (AVF) stenosis. *J Vasc Access* 2014; 15(1): 25–28. Juncos JP, Grande JP, Kang L, et al. MCP-1 contributes to arteriovenous fistula failure. *J Am Soc Nephrol* 2011; 22(1):43–48. https://doi.org/10.5301/jva.5000151.
6. Usman R, Jamil M and Naveed M. High preoperative neutrophil-lymphocyte ratio (NLR) and red blood cell distribution width (RDW) as independent predictors of native arteriovenous fistula failure. *Ann Vasc Dis* 2017; 10(3):205–210. https://doi.org/10.3400/avd.oa.17-00016.
7. Yilmaz H, Bozkurt A, Cakmak M, et al. Relationship between late arteriovenous fistula (AVF) stenosis and neutrophil-lymphocyte ratio (NLR) in chronic hemodialysis patients. *Ren Fail* 2014; 36(9): 1390–1394. 11. Akboga MK, 11. Canpolat U, Yuksel M, et al. Platelet to lymphocyte ratio as a novel indicator of inflammation is correlated with the severity of metabolic syndrome: a single center large-scale study. *Platelets* 2016; 27(2): 178–183. https://doi.org/10.3109/0886022X.2014.945183.
8. Akdag S, Akyol A, Asker M, et al. Platelet-to-lymphocyte ratio may predict the severity of calcific aortic stenosis. *Med Sci Monit* 2015; 21: 3395–3400. https://doi.org/10.12659/MSM.894774.
9. Horne BD, Anderson JL, John JM, et al. Which white blood cell subtypes predict increased cardiovascular risk? *J Am Coll Cardiol* 2005; 45(10): 1638–1643. https://doi.org/10.1016/j.jacc.2005.02.054.
10. Qin B, Ma N, Tang Q, et al. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. *Mod Rheumatol* 2016; 26(3):372–376. https://doi.org/10.3109/14397595.2015.1091136.
11. Ahbap E, Sakaci T, Kara E, et al. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in evaluation of inflammation in end-stage renal disease. *Clin Nephrol* 2016; 85(4): 199–208. https://doi.org/10.1186/s12882-020-02174-0.
12. Idil Soylu A, Arikan Cortcu S, Uzunkaya F, et al. The correlation of the platelet-to-lymphocyte ratio with the severity of stenosis and stroke in patients with carotid arterial disease. *Vascular* 2017; 25(3): 299–306. https://doi.org/10.1177/1708538116673770.
13. Milovanovic M, Nilsson E, Järemo P. Relationships between platelets and inflammatory markers in rheumatoid arthritis. Clin Chim Acta. 2004 May;343(1-2):237-40. https://doi.org/10.1016/j.cccn.2003.12.030.
14. Kilincalp S, Çoban Ş, Akinci H, Hamamcı M, Karaahmet F, Coşkun Y, et al. Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and mean platelet volume as potential biomarkers for early detection and monitoring of colorectal adenocarcinoma. Eur J Cancer Prev 2015;24:328-33. https://doi.org/10.1097/CEJ.0000000000000092
15. Kwon HC, Kim SH, Oh SY, Lee S, Lee JH, Choi HJ, et al. Clinical significance of preoperative neutrophil-lymphocyte versus platelet-lymphocyte ratio in patients with operable colorectal cancer. Biomarkers 2012;17:216-22. https://doi.org/10.3109/1354750X.2012.656705.
16. Kurtul A, Murat SN, Yarlioglues M, Duran M, Ergun G, Acikgoz SK, Demircelik MB, Cetin M, Akyel A, Kasapkara HA, Ornek E. Association of plateletto-lymphocyte ratio with severity and complexity of coronary artery disease in patients with acute coronary syndromes. Am J Cardiol. 2014 Oct 1;114(7):972-8. https://doi.org/10.1016/j.amjcard.2014.07.005.
17. Sarioglu O, Capar AE, Belet U. Relationship of arteriovenous fistula stenosis and thrombosis with the platelet-lymphocyte ratio in hemodialysis patients. J Vasc Access. 2020 Sep;21(5):630-635. https://doi.org/10.1177/1129729819894113.
18. Zhu F, Yao Y, Ci H, Shawuti A. Predictive value of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for primary patency of percutaneous transluminal angioplasty in hemodialysis arteriovenous fistula stenosis. Vascular.2022;30(5):920-927. https://doi.org/10.1177/17085381211039672.
19. Pasqui E, de Donato G, Lazzeri E, Molino C, Galzerano G, Giubbolini M, Palasciano G. High Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios Are Associated with a Higher Risk of Hemodialysis Vascular Access

Failure. Biomedicines. 2022 Sep 7;10(9):2218. https://doi.org/10.3390/biomedicines10092218.
20. Franchin M, Muscato P, Piffaretti G, Tozzi M. Systemic inflammation index as useful tool to predict arteriovenous graft stenosis: Our experience and literature review. The Journal of Vascular Access. 2024;25(2):474-480. https://doi.org/10.1177/11297298221119595.