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The Role of Systemic Inflammatory Markers in Arteriovenous Fistula Dysfunction – a State-of-the-Art Review

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ABSTRACT

Arteriovenous fistula (AVF) is the preferred method of vascular access for patients with end-stage kidney disease. However, excessive inflammation and inadequate remodeling of the venous component may cause intimal hyperplasia and AVF stenosis. This could lead to vascular access failure and an increased risk of mortality. Serum albumin, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein, mean platelet volume, platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index, interleukin-6, red cell distribution width, and fibrinogen have been identified as the most promising biomarkers in predicting AVF maturation and long-term patency. According to the 14 studies examined in this state-of-the-art review, with a total of 2,695 patients, NLR and PLR have shown the most promising prognostic role in terms of AVF outcome. Our findings indicate that systemic inflammatory indicators may be important in the development of dialysis-associated AVF dysfunction and warrant further evaluation of NLR and PLR as potential biomarkers for patient management and follow-up of AVF dysfunction.

Keywords: arteriovenous fistula, inflammatory biomarkers, stenosis, vascular access

INTRODUCTION

Arteriovenous fistula (AVF) is the first choice for vascular access in patients with end-stage kidney disease (ESKD).[1–4] The long-term permeability and favorable outcome of AVF depend on maintaining a balance between inflammation and repair during the venous wall remodeling process.[5,6] Excessive inflammation and impaired repair can lead to intimal hyperplasia (IH) and AVF stenosis, resulting in vascular access dysfunction for dialysis and an increased risk of mortality.[7] A recent study by Matsubara *et al.*[8] highlighted the critical role of inflammation in AVF remodeling and maturation by distinguishing the different functions of T cell and macrophage subsets.

Thus, recently a particular interest has been directed to the study and identification of some biomarkers with a prognostic role in AVF dysfunction, but without success in implementing a protocol for use in the management of vascular access.[9–11]

We conducted a state-of-the-art review to analyze and present the published data from the last decade on systemic inflammatory biomarkers and their impact on AVF dysfunction. Our aim was to investigate the impact of systemic inflammation on local remodeling and suggest new prevention strategies and risk stratification for a better management of vascular access.

SYSTEMIC INFLAMMATORY BIOMARKERS

After a detailed analysis of the literature from the last decade, the most promising biomarkers are serum albumin, the neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), mean platelet volume (MVP), the platelet-to-lymphocyte ratio (PLR), the systemic immune-inflammation index (SII), interleukin-6 (IL-6), red cell distribution width (RDW), and fibrinogen.[12–25] We analyzed the results of 14 studies with a total number of 2,695 patients, with an average age of 57.79 years, of which 1,655 (61.41%) were male. The patients' comorbidities included arterial hypertension in 77.45% of cases, followed by diabetes (41.47%, ischemic heart disease (32.07%), and peripheral arterial disease (16.41%), as well as active smoking as a risk factor in 40.64% of patients (Table 1).

The role of NLR was analyzed in six studies[13,14,17,22,23,25], that of PLR in four studies,[20,22,23,25] serum albumin in three studies12,16,18, CRP in three studies,[12,15,22] IL-6,[24,26] MPV,[19,21] and SII[22,25] in two studies each, and the role of fibrinogen[12] and RDW[14] in one study each (Tables 2 and 3). Further, we will present the results of inflammatory biomarkers from at least three studies.

NLR

In 2014, Yilmaz *et al.*[13] identified that high basal values of NLR are positively associated with the presence of AVF stenosis (odds ratio (OR) 6.61, p <0.001). In addition, they identified an optimal biomarker cut-off value of 2.7 with a sensitivity of 98.4% and a specificity of 75% in the receiver operating characteristic (ROC) analysis. Similarly, Usman *et al.*[14] validated the results of the previous study (OR 1.39, p <0.001) on a cohort of 300 patients, in which they followed AVF dysfunction 3 months postoperatively. The authors identified an optimal cut-off value of 2.65 with a sensitivity of 98% and a specificity of 80%. Furthermore, a third study, published by Wongmahisorn *et al.*,[17] identified a similar cut-off value of 2.7 (sensitivity of 82.6% and specificity of 52%) above which they demonstrated that there is a five times higher risk of AVF failure at 3 months (p = 0.005).

Recently, Kaller *et al.*[22,25] and Pasqui *et al.*[23] demonstrated that high NLR values are associated with maturation failure at 6–8 weeks and with long-term patents. A possible explanation of the mechanism was presented by Kaller

TABLE 1. Patient demographics and comorbidities from the included studies

Study	Year	Country	No. of patients	Mean age (years)	Male sex, n (%)	Hypertension, n (%)	Ischemic heart disease, n (%)	Diabetes, n (%)	Peripheral arterial disease, n (%)	Active smoking, n (%)
Kaygin *et al.*[12]	2013	Turkey	386	56.36	213 (55)	–	–	169 (43.78)	37 (9.5)	197 (51)
Yilmaz *et al.*[13]	2014	Turkey	108	55.2	56 (51.8)	–	35 (32.4)	–	–	31 (28.7)
Usman *et al.*[14]	2017	Pakistan	300	44	230 (76.6)	–	51 (17)	113 (37.6)	–	163 (54.3)
Stirbu *et al.*[15]	2017	Romania	258	59.7	155 (60.07)	145 (56.2)	152 (58.91)	81 (31.39)	55 (21.31)	101 (39.14)
Kordzadeh *et al.*[16]	2017	UK	195	68	144 (73.8)	159 (81)	41 (21)	73 (37)	–	–
Wongmahisorn *et al.*[17]	2019	Thailand	396	61.2	202 (51)	353 (89.1)	79 (19.9)	220 (55.6)	–	–
Martinez-Mier *et al.*[18]	2019	Mexico	82	36.3	61 (74.4)	74 (90.2)	–	11 (13.4)	–	15 (18.3)
Lano *et al.*[19]	2019	France	153	65.5	91 (59.47)	135 (88)	54 (35)	55 (35)	40 (26)	66 (43)
Sarioglu *et al.*[20]	2020	Turkey	95	57.51	51 (53.7)	64 (67.37)	–	34 (35)	–	–
Bilican *et al.*[21]	2020	Turkey	95	57.2	42 (44.2)	41 (43.15)	22 (23.15)	41 (43.15)	5 (5.26)	33 (34.73)
Kaller *et al.*[22]	2022	Romania	125	61.64	76 (60.8)	102 (81.6)	83 (66.4)	52 (41.6)	32 (25.6)	43 (34.4)
Pasqui *et al.*[23]	2022	Italy	178	67.5	120 (67.4)	150 (84.3)	63 (35.4)	36 (20.2)	16 (9)	26 (14.6)
Baek *et al.*[24]	2023	Korea	282	62	190 (67.37)	–	–	161 (57.09)	–	–
Kaller *et al.*[25]	2023	Romania	42	57.07	24 (57.14)	31 (73.81)	–	27 (64.29)	18 (42.86)	27 (64.29)

TABLE 2. Statistical analysis and parameters of the included studies

Study	AAA diameter (cm)	Study group value	Control group value	Cut-off value	AUC/ROC analysis	Sensitivity (%)	Specificity (%)	Outcome	Follow-up period
Kaygin *et al.*[12]	Albumin	3.0	3.96	–	–	–	–	Unsuccessful AVF	3 months
	CRP	18.6	4.6	–	–	–	–		
	Fibrinogen	530.5	348.9	–	–	–	–		
Yilmaz *et al.*[13]	NLR	3.47	2.27	2.7	0.893	98.4	75	AVF stenosis	–
Usman *et al.*[14]	NLR	3.3	2.2	2.65	0.792	98	80	AVF failure	3 months
	RDW	15.9	13.6	15.1	0.821	98	79		
Stirbu *et al.*[15]	CRP	3.24	0.54	–	–	–	–	AVF failure	26 months
Kordzadeh *et al.*[16]	Albumin	<35	≥35	–	–	–	–	AVF failure	–
Wongmahisorn *et al.*[17]	NLR	4.5	3.1	2.7	0.673	82.6	52	AVF failure	3 months
Martinez-Mier *et al.*[18]	Albumin	3.3	3.8	3.35	0.715	81	67.2	AVF failure	12 months
Lano *et al.*[19]	MPV	11.3	10.6	–	–	–	–	AVF failure	24 months
Sarioglu *et al.*[20]	PLR	284.87	120.24	68.37	0.646	88.9	98.9	AVF thrombosis	–
Bilican *et al.*[21]	MPV	8.6	7.8	–	–	–	–	AVF thrombosis	12 months
Kaller *et al.*[22]	NLR	5.9	2.86	4.9	0.856	81.1	84.1	Non–maturation	6 weeks
	PLR	208.39	140.59	172.29	0.74	70.3	73.9		
	SII	1,294.63	641.99	954.54	0.802	78.4	72.7		
	CRP	2.15	1.97	2.07	0.785	83.8	73.9		
Pasqui *et al.*[23]	NLR	8.27	3.55	4.21	0.7733	75	69.66	AVF failure	6 months
	PLR	266	194	208.8	0.6131	61.84	56.86		
Baek *et al.*[24]	IL-6	3.96	2.76	2.945	0.730	–	–	AVF failure	12 months
Kaller *et al.*[25]	NLR	5.71	2.47	–	–	–	–	Non–maturation	8 weeks
	PLR	244.25	109.55	–	–	–	–		
	SII	1644.3	561	–	–	–	–		
	IL-6	7.66	5.32	–	–	–	–		

et al.[25], who found a positive correlation between the inflammatory markers NLR, PLR, SII, and IL-6, and CD-31-positive relative surface at the level of the intima-media complex in the venous wall. Additionally, higher levels of inflammatory markers were recorded in patients who had intimal hyperplasia at the time of performing AVF.

PLR

Out of the four studies, only three conducted ROC analysis and determined an optimal cut-off value, revealing a noteworthy variation. Sarioglu *et al.*[20] reported a PLR cut-off value of 68.37 (sensitivity of 88.9% and specificity of 98.9%), Kaller *et al.*[22] reported a cut-off value of 172.29 (sensitivity of 70.3% and specificity of 73.9%), and Pasqui *et al.*[23] reported a cut-off value of 208.8 (sensitivity of 61.84% and specificity of 56.86%). This variability can be attributed to a higher prevalence of hypertension among patients in the studies by Kaller *et al.*[22] and Pasqui *et al.*[23], as well as the higher average age of patients. Additionally, the study of Sarioglu *et al.*[20] revealed through logistic regression analysis that PLR did not have a predictive role in AVF thrombosis and stenosis. Nevertheless, the other three studies identified PLR as a predictive factor for AVF dysfunction, with ORs ranging from 1.02 to 6.68 ($p < 0.05$ for all).

SERUM ALBUMIN AND CRP

Among the studies examining the role of serum albumin in AVF dysfunction, Kordzadeh *et al.*[16] (OR 0.48, $p = 0.043$) and Martinez-Mier *et al.*[18] (OR 0.29, $p = 0.03$) revealed that elevated serum albumin levels provide protection against AVF dysfunction at the 12-month follow-up. Additionally, Kaller *et al.*[22] observed lower albumin values in the group of patients with failure of AVF maturation at 6 weeks (2.93 vs. 3.78, $p < 0.0001$). Regarding the optimal cut-off value, only the study of Martinez-Mier *et al.*[18] presented ROC analysis results, indicating an area under the curve (AUC) of 0.715 with an albumin threshold value of 3.35 (sensitivity of 81% and specificity of 67.2%). Despite being a common biomarker and widely available in current practice, serum albumin has received limited attention in the context of vascular access. In the same way, two[15,22] of the

TABLE 3. The values of biomarkers in the included studies

Study	Biomarker	OR/HR	95% CI		p value	Kaplan–Meier	logrank p value
			Lower	Upper			
Yilmaz *et al.*[13]	NLR	6.61	3.567	8.912	<0.001	–	–
Usman *et al.*[14]	NLR	1.39	1.02	2.08	<0.001	–	–
	RDW	1.39	1.11	1.69	<0.001		
Stirbu *et al.*[15]	CRP	1.17	1.136	1.206	<0.001	AVF patency related to the cause of ESRD	0.007
Kordzadeh *et al.*[16]	Albumin	0.48	0.23	0.98	0.043	–	–
Wongmahisorn *et al.*[17]	NLR	5.16	3.05	8.74	0.005	–	–
Martinez-Mier *et al.*[18]	Albumin	0.29	0.09	0.93	0.03	–	–
Lano *et al.*[19]	MPV	1.58	1.17	2.14	0.003	VA events depending on the MPV quartile.	0.001
Sarioglu *et al.*[20]	PLR	1.009	0.991	1.0270	0.325	–	–
Bilican *et al.*[21]	MPV	2.83	1.593	5.025	0.001	–	–
Kaller *et al.*[22]	PLR	6.68	2.85	15.63	<0.001	–	–
	SII	9.66	3.88	24.07	<0.001		
	CRP	14.6	5.39	39.49	<0.001		
Pasqui *et al.*[23]	NLR	2.53	1.85	2.96	0.02	AVF patency based on NLR/PLR cut–off value	<0.0001
	PLR	2.37	1.64	2.76	0.04		
Baek *et al.*[24]	IL-6	3.12	1.24	7.87	0.016	AVF survival rate based on IL–6 tertiles	0.05
Kaller *et al.*[25]	NLR	2.61	1.43	4.78	0.002	–	–
	PLR	1.02	1.01	1.04	0.02		
	SII	1.003	1.001	1.006	0.04		
	IL-6	1.15	1.01	1.30	0.03		

three studies that analyzed the role of CRP in the evolution of AVF demonstrated that high values are associated with a reduced patent and maturation failure at 6 weeks.

SYSTEMIC INFLAMMATION IN THE PROCESS OF VENOUS REMODELING

The failure of AVF maturation arises from the development of IH and biomechanical alterations in the extracellular matrix of the vein wall. Endothelial injury, triggered by excessive vein dilatation under arterial pressure, stands out as a primary inducer of IH.[26] Consequently, endothelial cell injury, local inflammatory response, and the migration and proliferation of smooth muscle tissue contribute to venous wall thickening through an IH mechanism, leading to severe forms of AVF stenosis and dysfunction.[27,28] Current IH inhibition therapies have shown variable efficacy and are not widely adopted. Yang *et al.*[29] suggested stent implantation around the vein graft in a murine carotid bypass model with jugular vein interposition, demonstrating a positive correlation between limiting venous graft distension, inhibiting intimal hyperplasia, and reducing local inflammation.

Recent findings by Kaller *et al.*[25] complement these conclusions, revealing an association between systemic inflammation and the presence of IH. Future investigations should focus on analyzing how systemic inflammation impacts the local inflammatory response within the venous wall due to graft distension following exposure to arterial pressure.

CONCLUSIONS

Our research has shown that systemic inflammatory biomarkers play a significant role in the development of dialysis-associated AVF dysfunction. However, there is no defined optimal cut-off value, which requires further studies involving multiple centers with a long-term follow-up. Additionally, recent studies have revealed a connection between systemic inflammation and localized alterations in the venous wall, which significantly impact the mechanical properties of the tissue. Future studies can explore the biomechanical remodeling of the venous wall to gain new insights into the subject.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Schmidli J, Widmer MK, Basile C, et al. Editor's Choice - Vascular Access: 2018 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg*. 2018;55:757–818.
2. Arbanasi EM, Russu E, Muresan AV, Arbanasi EM, Kaller R. Ulnar-basilic arteriovenous fistula with multilocular gigantic aneurysmal dilatation: a case report. *Acta Marisiensis - Seria Medica*. 2021;67:244–246.
3. Kaller R, Mureșan AV, Arbănași EM, et al. Uncommon Surgical Management by AVF between the Great Saphenous Vein and Anterior Tibial Artery for Old Radiocephalic AVF Failure. *Life*. 2022;12:529.
4. Russu E, Muresan AV, Arbanasi EM, et al. Polytetrafluorethylene Prosthesis Interposition in Vascular Access. *Materiale Plastice*. 2022;59:1–8.
5. Duque JC, Tabbara M, Martinez L, Cardona J, Vazquez-Padron RI, Salman LH. Dialysis Arteriovenous Fistula Failure and Angioplasty: Intimal Hyperplasia and Other Causes of Access Failure. *Am J Kidney Dis*. 2017;69:147–151.
6. Martinez L, Duque JC, Tabbara M, et al. Fibrotic Venous Remodeling and Nonmaturation of Arteriovenous Fistulas. *J Am Soc Nephrol*. 2018;29:1030–1040.
7. Mureșan AV, Russu E, Arbănași EM, et al. The Predictive Value of NLR, MLR, and PLR in the Outcome of End-Stage Kidney Disease Patients. *Biomedicines*. 2022;10:1272.
8. Matsubara Y, Kiwan G, Fereydooni A, Langford J, Dardik A. Distinct subsets of T cells and macrophages impact venous remodeling during arteriovenous fistula maturation. *JVS Vasc Sci*. 2020;1:207–218.
9. Campos B, Lee T, Roy-Chaudhury P. Arteriovenous fistula failure: is there a role for epigenetic regulation? *Semin Nephrol*. 2013;33:400–406.
10. Gameiro J, Ibeas J. Factors affecting arteriovenous fistula dysfunction: A narrative review. *J Vasc Access*. 2020;21:134–147.
11. Morton SK, Rodríguez AJ, Morris DR, Bhandari AP, Moxon JV, Golledge J. A Systematic Review and Meta-Analysis of Circulating Biomarkers Associated with Failure of Arteriovenous Fistulae for Haemodialysis. *PLoS ONE*. 2016;11:e0159963.
12. Kaygin MA, Halici U, Aydin A, et al. The relationship between arteriovenous fistula success and inflammation. *Renal Failure*. 2013;35:1085–1088.
13. Yilmaz H, Bozkurt A, Cakmak M, et al. Relationship between late arteriovenous fistula (AVF) stenosis and neutrophil-lymphocyte ratio (NLR) in chronic hemodialysis patients. *Renal Failure*. 2014;36:1390–1394.
14. Usman R, Jamil M, 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;10:205–210.
15. Stirbu O, Gadalean F, Pitea IV, et al. C-reactive protein as a prognostic risk factor for loss of arteriovenous fistula patency in hemodialyzed patients. *J Vasc Surg*. 2019;70:208–215.
16. Kordzadeh A, Tokidis E, Askari A, Hoff M, Panayiotopoulos Y. The independent association of preoperative serum albumin on the functional maturation of radiocephalic arteriovenous fistulae. *J Vasc Access*. 2017;18:148–152.
17. Wongmahisorn Y. Role of neutrophil-to-lymphocyte ratio as a prognostic indicator for hemodialysis arteriovenous fistula failure. *J Vasc Access*. 2019;20:608–614.
18. Martinez-Mier G, Camargo-Diaz C, Urbina-Velazquez MA, Avila-Pardo SF. Predictive Factors for Unsuccessful Use of Arteriovenous Fistula in a Population of End-Stage Renal Disease Patients in Southeastern Mexico. *Ann Vasc Surg*. 2020;62:304–309.
19. Lano G, Sallée M, Pelletier M, et al. Mean Platelet Volume Predicts Vascular Access Events in Hemodialysis Patients. *J Clin Med*. 2019;8:608.
20. 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;21:630–635.
21. Bilican G, Oguz EG, Yayar O, et al. Usefulness of mean platelet volume as a biomarker for diagnosing arterivenosus fistulas thrombosis in routine hemodialysis patients. *Ann Med Res*. 2020;27:0895–0902.
22. Kaller R, Arbănași EM, Mureșan AV, et al. The Predictive Value of Systemic Inflammatory Markers, the Prognostic Nutritional Index, and Measured Vessels' Diameters in Arteriovenous Fistula Maturation Failure. *Life*. 2022;12:1447.
23. Pasqui E, de Donato G, Lazzeri E, et al. High Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios Are Associated with a Higher Risk of Hemodialysis Vascular Access Failure. *Biomedicines*. 2022;10:2218.
24. Baek J, Lee H, Yang T, et al. Plasma Interleukin-6 Level Predicts the Risk of Arteriovenous Fistula Dysfunction in Patients Undergoing Maintenance Hemodialysis. *J Pers Med*. 2023;13:151.
25. Kaller R, Russu E, Arbănași EM, et al. Intimal CD31-Positive Relative Surfaces Are Associated with Systemic Inflammatory Markers and Maturation of Arteriovenous Fistula in Dialysis Patients. *Journal of Clinical Medicine*. 2023;12:4419.
26. de Vries MR, Simons KH, Jukema JW, Braun J, Quax PHA. Vein graft failure: from pathophysiology to clinical outcomes. *Nat Rev Cardiol*. 2016;13:451–470.
27. Sadaghianloo N, Contenti J, Dardik A, Mazure NM. Role of Hypoxia and Metabolism in the Development of Neointimal Hyperplasia in Arteriovenous Fistulas. *Int J Mol Sci*. 2019;20:5387.
28. Brownson KE, Khosravi R, Lee SR, et al. Venous Mechanical Properties After Arteriovenous Fistulae in Mice. *J Surg Res*. 2020;248:129–136.
29. Yang Q, Lei D, Huang S, et al. Effects of the different-sized external stents on vein graft intimal hyperplasia and inflammation. *Ann Transl Med*. 2020;8:102.