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RESEARCH ARTICLE

Risk factors associated with long-term radio-cephalic arteriovenous fistula failure in dialysis patients

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Objective: The aim of this study is to analyze the risk factors associated with long-term radio-cephalic arteriovenous fistula failure in dialysis patients.

Methods: This retrospective observational study enrolled 81 patients diagnosed with end-stage kidney disease requiring arteriovenous fistula. Patients were categorized into two groups based on the long-term permeability of vascular access. The hospital's electronic database was used to collect demographic data, risk factors, comorbidities, pre-operative laboratory data, and pre-operative vascular mapping characteristics.

Results: Among the patients with arteriovenous fistula failure, we observed a lower incidence of men (p=0.009), a higher incidence of diabetes mellitus (p=0.036), and a higher incidence of active smoking (p=0.009). At ROC-curve analysis we identified an optimal cut-off value of 128.2 for glucose (AUC: 0.715, 66.7% Sensitivity, and 78.1% Specificity), 1.17 for leukocyte glucose index (AUC: 0.692, 60.0% Sensitivity, and 81.2% Specificity), and 7.33 for interleukin-6 (AUC: 0.925, 90.0% Sensitivity, and 84.6% Specificity). In Kaplan-Meier survival curve analysis, there was a higher incidence of arteriovenous fistula failure among females (p=0.033), smokers (p<0.001), and patients undergoing hemodialysis via a central venous catheter at the time of admission (p=0.047). Cox-regression analysis indicates that female sex (HR: 3.43, p=0.033) and active smoking (HR: 5.02, p=0.002) are predictors of vascular access dysfunction. Additionally, elevated values of glucose (HR: 1.89, p=0.004), Interleukin-6 (HR: 2.78, p=0.001), and leukocyte glucose index (HR: 1.95, p=0.008) are associated with arteriovenous fistula failure.

Conclusions: In conclusion, female sex, active smoking, high baseline glucose levels, Interleukin-6, and leukocyte glucose index are linked to long-term failure of arteriovenous fistula failure.

Keywords: leukocyte glucose index, vascular surgery, arteriovenous fistula, dialysis, interleukin-6

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Introduction

Autologous arteriovenous fistula (AVF) is the recommended vascular access for dialysis according to the guidelines of the European Society of Vascular Surgery (ESVS) in end-stage kidney disease (ESKD) patients [1]. Also, AVF has better long-term patency compared to arteriovenous fistula graft (AVG) [1–3] and a lower mortality rate compared to a central venous catheter (CVC) [4]. However, the long-term functionality of AVF is affected by factors such as the site of surgical creation, the quality of the venous wall, systemic inflammation, and the presence of risk factors like diabetes, smoking, and cardiac comorbidities [1,4–7].

In a recent study published by Muresan et al. [4], the authors observed a significantly higher incidence of tobacco (66.67% vs 39.03%, p<0.0001) and elevated values of inflammatory markers (for all p<0.0001) in patients with ESKD whit poor outcome at 30 days. The same authors confirmed the aforementioned results in a study where they monitored AVF maturation failure within a cohort of 125 patients [5]. More recently, Muresan et al. [7] demonstrated a correlation between elevated leukocyte glucose index (LGI) values (HR:1.48, 95%CI 1.14-1.92, p=0.003) and long-term vascular access failure.

The primary objective of vascular access for dialysis is to establish a distal AVF in the non-dominant limb, between the radial artery and the cephalic vein (RC-AVF), if the vessel meets the quality criteria [1,5,6,8]. In the long term, RC-AVF presents a lower risk of steal syndrome [1,9,10] and aneurysmal development [1,9,10] compared to brachio-cephalic AVF (BC-AVF), but with a higher rate of maturation failure and primary and secondary pa-

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tency [1,11–13]. Also, the presence of a dialysis CVC has a negative impact on the long-term functionality of the AVF [1,14], regardless of the type of AVF performed [14]. According to literature studies, the maturation failure rate for RC-AVF is between 5-46%, and the secondary patency rate at 1 year is between 42-83% [1,15–18].

The primary aim of this study is to analyze the risk factors associated with long-term RC-AVF failure in dialysis patients. Additionally, we will investigate the role of inflammatory markers in AVF dysfunction and the impact of pre-operative vascular mapping.

Methods

Study Design

This retrospective and observational study includes all patients with ESKD who were hospitalized in the Vascular Surgery Clinic at Târgu Mureș County Clinical Hospital between January 2019 and August 2023 for an RC-AVF surgical creation. Patients who were hospitalized for existing AVF dysfunction, those with a septic state, autoimmune diseases, and those for whom information was not available in the hospital's electronic database were excluded. The patients were divided into two groups based on long-term AVF outcomes: "Functional AVF" and "AVF Failure". This study was approved by the Medical Ethics Committee for the Clinical Study of Medicines of the County Emergency Clinical Hospital Târgu Mureș, decision number 21407/09.10.2023.

Data Collection

The hospital's electronic database was used to collect demographic data, risk factors, comorbidities, pre-operative laboratory data, and pre-operative vascular mapping characteristics. We monitored for the presence of cardiovascular pathologies, diabetes mellitus, chronic obstructive pulmonary disease (COPD), obesity, and active smoking. Additionally, we recorded pre-operative laboratory analyses and calculated systemic inflammatory markers such as LGI [7], neutrophil to lymphocyte ratio (NLR) [4–6,19], platelets to lymphocyte ratio (PLR) [4–6], monocyte to lymphocyte ratio (MLR) [4,20], and derived neutrophil to lymphocyte ratio (dNLR) [19] (Table I). Additionally, the Interleukin-6 (IL-6) values were available only for 42 patients. During pre-operative vascular mapping, we recorded the diameter of the radial artery, the cephalic vein, and the depth of the cephalic vein. We also noted whether the RC-AVF was performed in the non-dominant limb or if the patients were undergoing dialysis at the time of admission. All patients in the study were either in outpatient settings or were hospitalized overnight for cost-effectiveness benefit [21].

Study Outcomes

The primary outcome of the study was to identify the risk factors linked to the long-term failure of RC-AVF. Additionally, we examined the influence of systemic inflammatory markers and the impact of dialysis via CVC at the time of admission on the dysfunction of dialysis vascular access. AVF permeability data was collected from the chronic dialysis centers where the patients are receiving treatment.

Statistical analysis

For the statistical analysis, we are using SPSS for Mac OS version 29.0.2.0 (SPSS, Inc. in Chicago, IL, USA). The mean values and standard deviations were used to present the laboratory data and pre-operative vascular mapping characteristics. We compared characteristics between groups using chi-square tests for dichotomous variables. Additionally, we used Mann-Whitney and Student's t-tests to assess differences between continuous variables. ROC curve analysis was utilized to determine the best cut-off values for glucose, interleukin-6, and LGI in relation to the risk of AVF failure.

We conducted multivariate Cox proportional hazard analyses to find independent predictors of RC-AVF failure in dialysis patients. Additionally, the hazard ratio (HR) was expressed per 1 standard deviation increase in the baseline for all analyzed laboratory data. We used Kaplan-Meier curves to show the crude association between demographic data, diabetes mellitus, active smoking, and CVC hemodialysis at the time of admission and long-term RC-AVF failure. To compare the curves, we used the Log Rank test. All tests were two-tailed, and a p-value less than 0.05 was considered statistically significant.

Results

In this study, we included 81 patients with RC-AVF who met all the criteria. The average age of the patients was 60.66±14.30, with 44 being men (54.32%) and 37 being women (45.68%). Among the most common comorbidities, according to the data presented in Table II, we found that 81.48% of patients had hypertension, 55.56% had ischemic heart disease, and 39.51% had diabetes mellitus. At the time of admission, 39 patients were not yet undergoing hemodialysis, and 13 patients had undergone RC-AVF in the dominant upper limb. In terms of pre-opera-

Table I. Formulas used for the systemic inflammatory biomarkers analyzed in this study.

Inflammatory Biomarkers	Formulas
Leukocyte glucose index (LGI)	(WBC count * Glucose level) / 1000
Neutrophil to Lymphocyte ratio (NLR)	Neutrophils count / Lymphocytes count
Platelets to Lymphocyte ratio (PLR)	Platelets count / Lymphocytes count
Monocyte to Lymphocyte ratio (MLR)	Monocytes count / Lymphocytes count
Derived Neutrophil to Lymphocyte ratio (dNLR)	Neutrophils count / (WBC count - Neutrophils count)

tive vascular mapping, we found that the average diameter of the radial artery was 2.94±0.86, the average diameter of the cephalic vein was 2.95±0.65, and the average depth of the cephalic vein was 2.56±0.78.

Furthermore, among the patients experiencing AVF failure, a significantly lower prevalence of males was noted (25.00% vs 61.54%, p=0.009). Additionally, there was a notably higher prevalence of diabetes mellitus (62.50% vs 33.85%, p=0.036) and active smoking (37.50% vs 10.77%, p=0.009) (Table II). With respect to the laboratory data, we observed elevated levels of glucose (p=0.010), LGI (p=0.021), and interleukin-6 (p<0.001) in patients exhibiting vascular access dysfunction. While we did not observe significant statistical differences in the pre-operative vascular mapping determinations, we did note a higher incidence of pre-dialysis patients among those with functional RC-AVF (Table II).

In the ROC analysis, we found a positive association between the glucose level at admission, the pre-operative values of LGI and IL-6, and long-term RC-AVF Failure (Figure 1). We identified an optimal cut-off value of 128.2 for glucose (Area under curve (AUC): 0.715, 66.7% Sensitivity, and 78.1% Specificity), 1.17 for LGI (AUC: 0.692, 60.0% Sensitivity, and 81.2% Specificity), and 7.33 for IL-6 (AUC: 0.925, 90.0% Sensitivity, and 84.6% Specificity) (Figure 1). The findings indicate that both glucose levels and inflammatory markers represent statistically significant and clinically actionable thresholds for identifying patients at an elevated risk of AVF failure.

Furthermore, in Kaplan-Meier survival curve analysis, there was a higher incidence of AVF failure among female patients (p=0.033), smokers (p<0.001), and patients undergoing hemodialysis via a CVC at the time of admission (p=0.047) (Figure 2).

We conducted a cox-regression analysis to determine which factors predict long-term RC-AVF failure. The analysis revealed that female sex (HR: 3.43, p=0.033) and active smoking (HR: 5.02, p=0.002) are predictors of vas-

Table II. Demographic data, associated comorbidities, and laboratory data of the enrolled patients.

Variables	All Patients n=81	Functional AVF n=65	AVF Failure n=16	p value
Age mean ± SD	60.66±14.30	60.69±14.54	60.56±13.71	0.973
Male no. (%)	44 (54.32%)	40 (61.54%)	4 (25.00%)	0.009
Comorbidities and Risk factors, no. (%)				
Hypertension	66 (81.48%)	55 (84.62%)	11 (68.75%)	0.143
Ischemic Heart Disease	45 (55.56%)	36 (55.38%)	9 (56.25%)	0.950
Atrial Fibrillation	6 (7.41%)	3 (4.62%)	3 (18.75%)	0.053
Cardiovascular events	4 (4.94%)	3 (4.62%)	1 (6.25%)	0.787
Cerebrovascular events	6 (7.41%)	3 (4.62%)	3 (18.75%)	0.053
Diabetes Mellitus	32 (39.51%)	22 (33.85%)	10 (62.50%)	0.036
Chronic Obstructive Pulmonary Disease	7 (8.64%)	5 (7.69%)	2 (12.50%)	0.540
Peripheral Arterial Disease	9 (11.11%)	6 (9.23%)	3 (18.75%)	0.278
Obesity	17 (20.99%)	14 (21.54%)	3 (18.75%)	0.806
Active Smoking	13 (16.05%)	7 (10.77%)	6 (37.50%)	0.009
Laboratory data, mean ± SD				
WBC	8.36±2.37	8.33±2.44	8.50±2.12	0.534
BUN (mg/dL)	137.94±56.42	139.32±58.05	131.71±49.87	0.658
Creatinine (mg/dL)	6.58±2.65	6.62±2.75	6.41±2.23	0.912
Eosinophils x10^3/uL	0.27±0.26	0.29±0.28	0.18±0.11	0.204
Potassium (mmol/L)	5.26±0.86	5.19±0.87	5.57±0.81	0.109
Sodium (mmol/L)	139.34±3.38	139.44±3.55	138.96±2.68	0.535
Glucose (mg/dL)	118.29±36.64	112.45±32.42	143.2±43.93	0.010
Hemoglobin g/dL	10.26±1.99	10.29±2.02	10.10±1.92	0.772
Hematocrit %	31.41±6.21	31.58±6.40	30.66±5.38	0.753
Neutrophils x10^3/uL	5.69±1.87	5.71±1.87	5.66±1.94	0.995
Lymphocytes x10^3/uL	1.64±0.71	1.65±0.69	1.58±0.85	0.575
Monocyte x10^3/uL	0.64±0.25	0.65±0.26	0.64±0.22	0.671
PLT x10^3/uL	242.35±79.55	236.51±76.33	267.72±90.69	0.175
LGI	0.99±0.42	0.93±0.37	1.24±0.53	0.021
Interleukin-6 (pg/mL)*	6.54±2.48	5.68±2.01	9.28±1.79	<0.001
NLR	4.07±2.27	3.97±2.19	4.50±2.63	0.662
PLR	170.91±89.41	159.59±62.35	219.95±155.46	0.158
MLR	0.45±0.21	0.44±0.20	0.48±0.25	0.522
dNLR	2.38±1.09	2.36±1.05	2.48±1.29	0.848
Pre-operative Vascular Mapping, mean ± SD				
Radial Artery Diameter	2.94±0.86	2.97±0.81	2.74±1.15	0.119
Cephalic Vein Diameter	2.95±0.65	3.01±0.68	2.65±0.29	0.151
Cephalic Vein Depth	2.56±0.78	2.54±0.74	2.66±1.12	0.722
Dominant Upper Limb, no. (%)	13 (16.05%)	9 (13.85%)	4 (25.00%)	0.276
Pre-Dialysis, no. (%)	39 (48.15%)	35 (53.85%)	4 (25.00%)	0.018

* Value of Interleukin-6 is available only for a group of 42 patients from entire cohort.

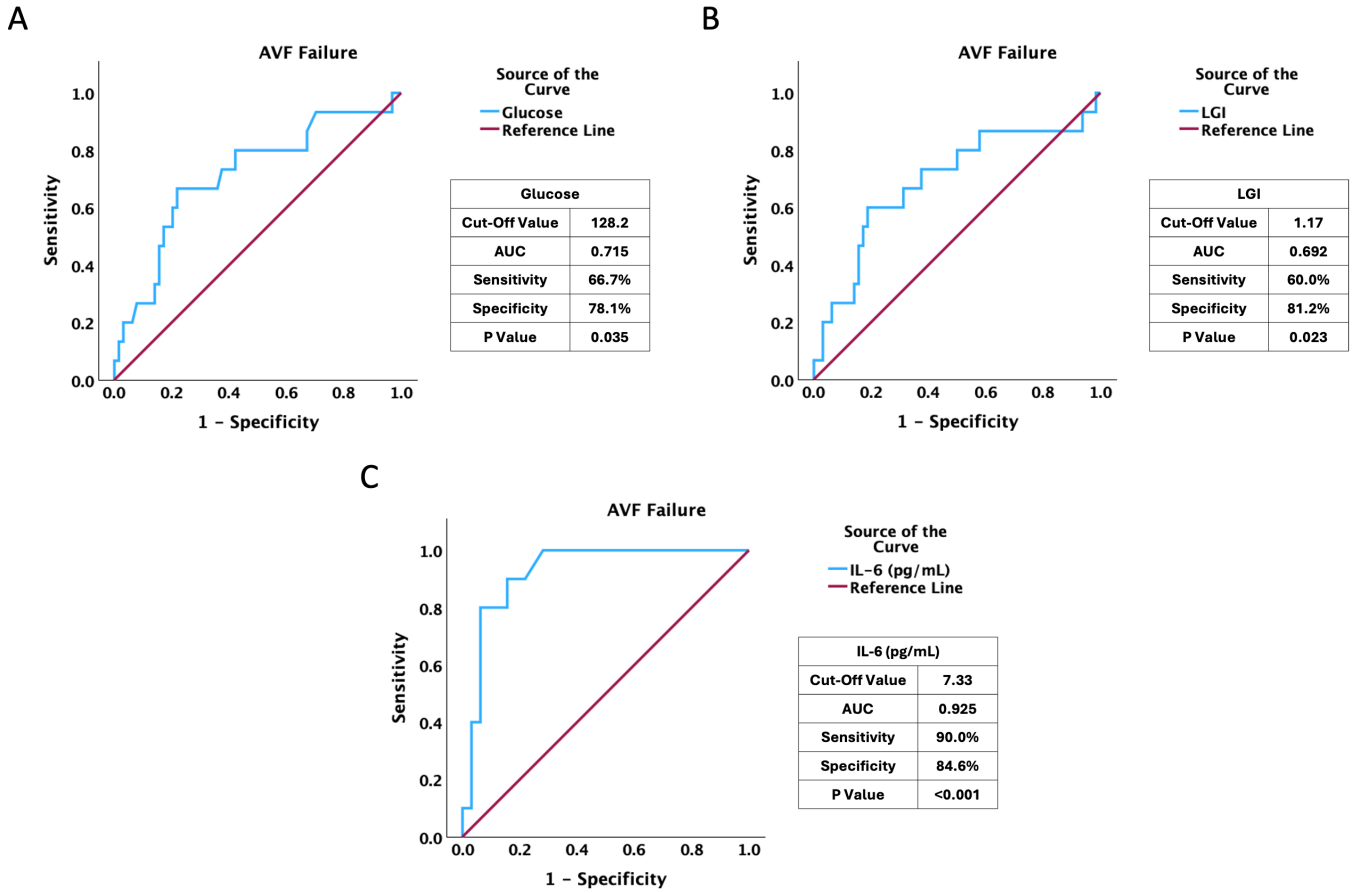

Fig. 1. ROC analysis of long-term RC-AVF failure in relation to: Glucose levels (A), LGI (B), and IL-6 (C).

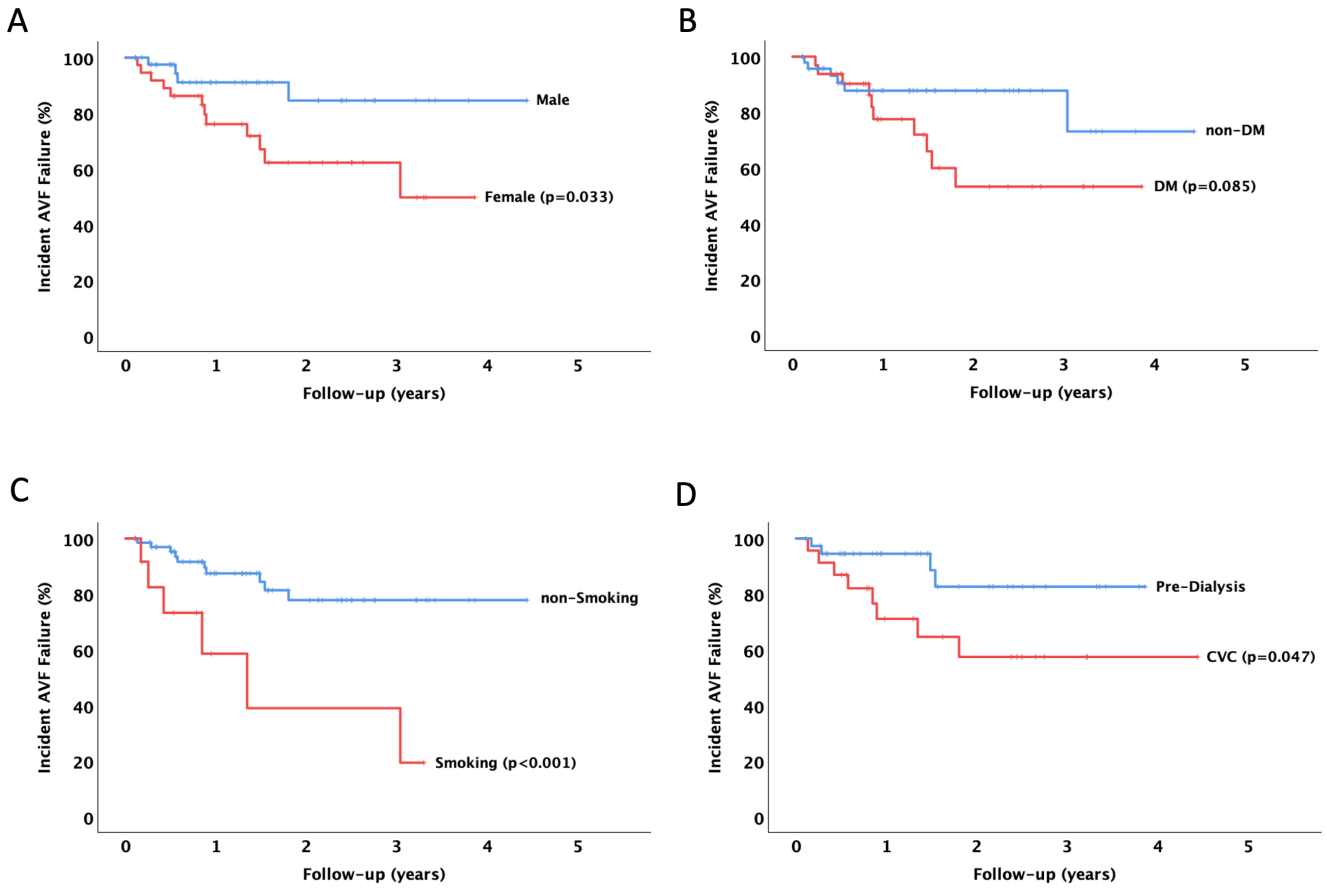

Fig. 2. Kaplan-Meier survival curves for the incidence of AVF failure in the entire cohort by: sex (A), diabetes mellitus (B), smoking status (C), and hemodialysis via a CVC at the time of admission (D). The p-value was calculated using an unadjusted log-rank test.

cular access dysfunction (Table III). Additionally, elevated basal values of glucose (HR: 1.89, p=0.004), IL-6 (HR: 2.78, p=0.001), and LGI (HR: 1.95, p=0.008) are associated with RC-AVF failure. Our findings emphasize the importance of systemic inflammation and metabolic dysfunction in the long-term failure of RC-AVF.

Discussions

The primary finding of this study is that females, active smoking, and high baseline levels of glucose, IL-6, and LGI are linked to long-term failure of RC-AVF. Moreover, patients experiencing vascular access dysfunction for dialysis have a high prevalence of diabetes mellitus and are often undergoing hemodialysis with a CVC at the time of AVF creation.

Similar to the results of our study, Miller et al. [22], Peterson et al. [23], and See et al. [24] observed that female patients have an increased risk of maturation failure and early and long-term AVF dysfunction. Another well-known risk factor of AVF failure is diabetes mellitus, and this was demonstrated by us in previously published studies [5–7], as well as in recent studies published in the literature [25–27]. In a meta-analysis by Yan et al. [25], the authors showed that the incidence of AVF failure is higher in diabetic patients compared to non-diabetic individuals (OR: 1.682, p<0.001). Additionally, Afsar and Elsurer [26] demonstrated that poor glycemic control (OR: 2.785, p=0.002) is the basis of the link between the presence of diabetes and AVF dysfunction. Smoking is also associated with unfavorable outcomes for both AVF [27,28] and ESKD patients [4].

Regarding inflammatory biomarkers, IL-6 has been the most frequently analyzed in AVF failure, while LGI is the most recently proposed biomarker. Kaller et al. [6] found that basal levels of IL-6 are increased in patients with intimal hyperplasia in the venous wall (p=0.0001) and are positively associated with neovascularization in the neointima (r=0.611, p<0.001). Baek et al. [29] observed that patients with baseline IL-6 values in tertile 3 (T3) have a three times higher risk of AVF dysfunction at one year (HR: 3.06, p=0.015). Marrone et al. [30] also demonstrated that local activation of IL-6 signaling is associated with AVF stenosis. In a recent study by Mureșan et al. [7], high pre-operative LGI values were associated with AVF dysfunction independent of sex, age, cardiovascular risk factors, and pre-operative vascular mapping characteristics.

In the current study, we identified an increased risk of AVF failure in patients undergoing hemodialysis on CVC at admission, but in the cox-regression analysis, the statistical significance was not maintained (p=0.062). Nevertheless, a study by Ravani et al. [31] showed that the use of CVC at the start of dialysis (p=0.0005) and the time from surgical creation to maturation (p=0.0007) are linked to an increased incidence of primary patency failure of AVF in a cohort of 414 patients.

Although the ESVS guidelines recommend the RC-AVF as the primary intention, this specific type of AVF is associated with elevated failure rates in terms of maturation and long-term patency [1]. Consequently, various techniques have been developed to enhance the patency of RC-AVF, such as the no-touch technique (NTT) and the modified no-touch technique (MNTT) [32]. A systematic review published by Bhojani et al. [33] demonstrated that nonconventional techniques, including NTT and MNTT, positively influence the long-term survival rates of RC-AVF. Furthermore, Inagaki et al. [34] introduced the resistance index (RI) as a novel prognostic tool for predicting AVF failure and established that a higher postoperative RI value is correlated with vascular access dysfunction. Regarding preoperative vascular mapping, Jiang et al. [35] illustrated that the diameter disparity between the radial artery and cephalic veins positively correlates with the primary patency of RC-AVF.

The current study has certain limitations that should be mentioned. Firstly, we only included patients with RC-AVF, so our findings may not apply to other types of AVF. Secondly, this was a retrospective study conducted at a single center with a small group of patients. We suggest that future research should involve larger, multicenter, prospective studies to provide more reliable conclusions. Additionally, all patients received surgical AVF, and we did not include those with percutaneous AVF. Lastly, AVF dysfunction was assessed by contacting chronic dialysis centers, and we were unable to evaluate the risk of aneurysmal development of the AVF or the extent of intimal hyperplasia using doppler ultrasound. We recommend periodic patient evaluations in the future to assess the risk of stenosis and aneurysmal development of the AVF.

Table III. Association between demographic data, comorbidities, preoperative laboratory parameters, and long-term outcomes of RC-AVF failure.

Variables	RC-AVF Failure		
	HR	95% CI	p value
Female	3.43	1.10-10.64	0.033
Diabetes Mellitus	2.51	0.91-6.93	0.075
Active Smoking	5.02	1.79-14.02	0.002
Pre-Dialysis	0.32	0.09-1.06	0.062
Glucose	1.89#	1.22-2.93	0.004
IL-6*	2.78#	1.51-5.14	0.001
LGI	1.95#	1.19-3.21	0.008

HR expressed per 1 SD increase in baseline; * The value of IL-6 is available only for a group of 42 patients from the entire cohort.

Conclusion

In conclusion, female sex, active smoking, and high baseline levels of glucose, IL-6, and LGI are linked to long-term failure of RC-AVF. Moreover, patients experiencing vascular access dysfunction for dialysis have a high prevalence of diabetes mellitus and are often undergoing hemodialysis with a CVC at the time of AVF creation.

Authors' contribution

AVM (Conceptualization; Methodology; Visualization; Writing – original draft; Supervision; Validation)
BR (Conceptualization; Formal analysis; Investigation; Resources)
Emil-Marian A (Conceptualization; Methodology; Formal analysis; Software; Writing – original draft; Validation)
Eliza-Mihaela A (Writing – review & editing; Formal Analysis; Validation)
ALS (Formal analysis; Investigation; Resources; Validation)
EF (Data curation; Investigation; Resources; Validation)
CMC (Investigation; Resources; Validation)
MMH (Formal analysis; Investigation; Validation)
IH (Data curation; Formal analysis; Supervision; Validation)
CCC (Formal analysis; Software; Data curation; Validation)
NAL (Data curation; Investigation; Validation)
IGB (Data curation; Investigation; Validation)
ER (Project administration; Methodology; Validation; Visualization; Supervision)

Conflict of interest

None to declare.

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