

The effect of preprocedural serum albumin to fibrinogen ratio on arteriovenous fistula maturation

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Ethics Committee Approval

Ethical Committee of Evliya Çelebi Training and Research Hospital, 55719891/604.02.94
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest

No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Inflammation and inflammatory parameters are known to have unfavorable effects both on the surgical success and survival. The reference point of the present study are the results of an investigation of the effects of blood proteins such as albumin and fibrinogen, which affect blood viscosity, and other hematological parameters, on the success of arteriovenous fistula operations.

Methods: This retrospective cohort study includes the data of 135 patients who underwent arteriovenous fistula surgery by the same surgeon in the same center. The patients were divided into two groups, as those with an active fistula 8–12 weeks after surgery and those with a dysfunctional fistula. After applying the exclusion criteria, the remaining data were compared using appropriate statistical methods to evaluate the influence on fistula maturation rates.

Results: A statistical analysis performed after the evaluation of the fitness of the data to a normal distribution revealed fistula maturation to be associated with fibrinogen ($P<0.001$), albumin ($P<0.001$), fibrinogen-to-albumin ratio (FAR) ($P<0.001$) and neutrophil-to-lymphocyte ratio (NLR) ($P=0.002$). It was further noted that C-reactive protein (CRP) ($P<0.001$), CRP-to-albumin ratio (CAR) ($P<0.001$), neutrophil count ($P=0.003$) and lymphocyte count ($P=0.03$) all played a role in this process. A receiver operating characteristic (ROC) curve analysis revealed the cut-off values for fibrinogen ($P<0.001$, AUC: 0.930), CRP ($P<0.001$, AUC: 0.892), FAR ($P<0.001$, AUC: 0.988), CAR ($P<0.001$, AUC: 0.916), neutrophil count ($P=0.011$, AUC: 0.661) and albumin ($P<0.001$, AUC: 0.946) in terms of fistula maturation.

Conclusion: The present study reveals that low albumin and high fibrinogen levels negatively affect AVF maturation. As reported previously in literature, and supported by the present study, high CRP levels may be associated with early AVF dysfunction.

Keywords: Arteriovenous fistula, Albumin, Fibrinogen, AV fistula, NLR, Neutrophil to lymphocyte ratio

Introduction

Hemodialysis catheters (HDCs) and autologous arteriovenous fistulas (AVFs) are the most popular methods for the delivery of hemodialysis to patients with end-stage renal failure (ESRF). Among these, HDC is not the first choice, given the risk of infection, stenosis in the central veins and intracardiac thrombus. The creation of an AVF is the approach to vascular access recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative, as well as the European Society of Vascular Surgery: 2018 Vascular Access Clinical Practice guidelines, due to its high patency rates, low morbidity and mortality, and high patient comfort [1]. Among the leading disadvantages of AVFs, however, is the maturation period, and furthermore, an appropriate-diameter venous system and an intact arterial system are required for the creation of a successful AVF. Studies have found that the primary reason for early AVF failures are venous pathologies [2]. The long maturation period, the potential for early AVF dysfunction and the resulting need to insert an HDC can be counted among the disadvantages of AVFs [3].

The idea that hematological parameters may be involved in the AVF maturation process, affecting AVF patency, and the physical characteristics of vascular structures, have led to various studies in this field. High CRP levels and a high NLR have been identified as poor prognostic markers in many diseases [4-6].

Despite the number of studies of inflammatory markers, the reference point of the present study is the lack of studies examining the hematological parameters [7] that constitute the gross mass of the blood and that affect blood viscosity, such as albumin and fibrinogen. The present study hypothesizes that hemoconcentration may be associated with early AVF dysfunction, and focuses particularly on albumin and fibrinogen, while reproducing previously reported findings for CRP and NLR.

Materials and methods

Study design and patient selection

After making the required application to the local ethics committee (Evliya Celebi Training and Research Hospital, 55719891/604.02.94), the data of patients who underwent AVF creation between 2015 and 2019 were reviewed, and those who underwent successful radiocephalic (Brescia-Cimino) AVF creation by the same surgeon were included in the study. Patients who underwent fistula creations using approaches other than the Brescia-Cimino technique, those with missing hematological parameters, those receiving steroids and those with evidence of an active infection were excluded from the study. Due to the retrospective nature of the study, there was no need to obtain informed consent from the patients.

Patients who are to undergo fistula creation operations in the study center are admitted on the operation day. Blood samples are collected on the same day as the operation and analyzed in the hospital's laboratory. The study data derives from the blood samples drawn on operation day.

The patients were discharged after the AVF operation, and after being weighed, they were placed on a 5-day course of enoxaparin sodium therapy at half the recommended dose for patients without ESRD (0.5 mg/kg, 2x1). At the time of the

outpatient control visit (6–12 weeks after surgery), the patients were divided into two groups depending on the maturation of the fistula: Patent fistula (Group 1) and fistula failure (Group 2). The parameters used to determine the maturation of AVF were the presence of a thrill sensation and audible bruit extending along the adequate length, a superficialized and easily compressible vein, a minimum 600 mL/min AVF flow rate, and an at least 6 mm internal diameter and a maximal 6 mm depth from the skin to the outflow vein upon Doppler ultrasound measurement [8]. No follow-up data in the late term was examined, as the focus of the present study was on early outcomes. In patients with subclavian vein HDC, care was taken not to open the AVF from the same side.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics (Version 22.0. Armonk, NY: IBM Corp.). The initial analysis ascertained whether the variables differed across the study groups, and the outliers of each variable were excluded. In the comparison of mean values, it was found that:

i) The dependent variable between the groups was continuous,

ii) The dependent variable showed a normal distribution in the two groups. It was therefore decided to perform a t test, for which the homogeneity of variance was assumed. A correction was made to the SD value if the variances were not homogeneous.

After the correction was made:

- a Chi-square test was performed if assumption “i” was not met; in other words, if the dependent variable was continuous (binary data).

- A non-parametric Mann-Whitney U-test was used if the assumption “ii” was not met.

Control for outliers was made only for continuous variables, and the missing values were deleted in a pairwise manner in all analyses (not the entire unit, but only the pairs). A *P*-value of less than 0.05 was considered statistically significant.

ROC curves were drawn to calculate the AUC and cut-off values of the fibrinogen, albumin, FAR, CRP, CAR, neutrophil count, and lymphocyte count for AVF maturation.

Results

A demographic analysis revealed 60 patients (44%) to be female, and an overall mean age of 56.48 (13.6) years.

At the 6–12-week outpatient control visit, the fistula was dysfunctional in 29 patients (22%) (Group 2). The characteristics of the patients are presented in Table 1. It was concluded that high CRP, fibrinogen, neutrophil count, and lymphocyte count in blood samples collected prior to the procedure were associated with AVF dysfunction, while other parameters, including triglyceride, HDL, LDL, gender, age, or the presence of DM, HT, COPD, smoking and history of MI were not. Albumin values were significantly lower in Group 2 (Tables 1 and 2).

A logistic regression analysis was performed to evaluate the effects of fibrinogen, albumin, CRP, FAR and CAR on the dependent variable of fistula function, in which significant differences were observed between the groups, and were found to be of diagnostic significance.

The ROC curve analysis revealed the cut-off values for fibrinogen ($\alpha=0.01$, AUC=0.930 and $P<0.001$, cut off: 451), CRP

($\alpha=0.01$, AUC=0.892 and $P<0.001$, cut-off: 7.20), FAR ($\alpha=0.01$, AUC=0.988 and $P<0.001$, cut-off: 147), CAR ($\alpha=0.01$, AUC=0.916 and $P<0.001$, cut-off: 2.494), neutrophil ($\alpha=0.01$, AUC=0.661 and $P=0.011$) and lymphocyte ($\alpha=0.01$, AUC=0.603 and $P=0.100$) count, which had an inverse relationship with AVF maturation (Figure 1), and albumin ($\alpha=0.01$, AUC=0.946 and $P<0.001$, cut-off: 3,15) and NLR ($\alpha=0.01$, AUC=0.634 and $P=0.048$), which had a direct relationship with AVF maturation (Figure 2).

Table 1: The characteristics of the patients

Variables	Successful AVF (n=106)	Unsuccessful AVF (n=29)	P-value
Age, mean (SD)	59.2(19.6)	61.8 (16.3)	0.487%
Gender			
Female	48 (46%)	12 (42%)	0.776*
Male	58 (54%)	17 (58%)	
Median weight (kg)	72(4.4)	74(3.7)	0.436 [§]
BMI (kg/m ²)	22.4(2.4)	22.9 (3.2)	0.223 [§]
DM (n, %)	44 (42%)	14 (48%)	0.456*
HT (n, %)	22 (21%)	6 (20%)	0.958*
COPD (n, %)	24 (22%)	7 (24%)	0.865*
Smoking (now or recent)	50 (47%)	15 (51%)	0.664*
MI History (n, %)	9 (8%)	3 (10%)	0.720*
BUN (mg/dL)	114(28)	109 (30)	0.198 [§]
Creatinine (mg/dL)	4.4(1.9)	4.2(2.1)	0.107 [§]

*Student t test, * X² Test, § Mann Whitney U Test

Table 2: Hematologic parameters of the patients

	Successful AVF (n=106)	Unsuccessful AVF (n=29)	P-value
Albumin (g/dL)	3.65(0.5)	2.8(0.7)	<0.001 [§]
Fibrinogen (mg/dL)	322.6 (92.2)	533.7 (165.2)	<0.001 [§]
CRP (mg/dL)	3.8 (1.7)	15.2 (4.4)	<0.001 [§]
Total protein (g/dL)	6.9(0.2)	6.7(0.5)	0.359 [§]
Triglyceride (mg/dL)	159.7 (75.8)	150.1 (80.2)	0.120%
Total Cholesterol (mg/dL)	177.2(39.5)	182.2 (41.1)	0.549%
LDL Cholesterol (mg/dL)	120.5 (22.4)	125.9(30.4)	0.111%
HDL Cholesterol (mg/dL)	33.9(9.2)	32.1 (8.9)	0.914%
Neutrophil (10 ³ /uL)	5.36(0.35)	6.1(1.26)	0.003%
Lymphocyte (10 ³ /uL)	1.49(0.19)	1.65(0.35)	0.030%
CAR	1.69 (2.5)	0.38 (0.6)	<0.001 [§]
FAR	90.81(26.27)	211.57(86.44)	<0.001 [§]
NLR	3.653 (0.82)	3.289(0.39)	0.002 [§]

* Student t Test, § Mann Whitney U Test

Figure 1: ROC curve analysis for hematological parameters which show inverse relationship with AVF maturation

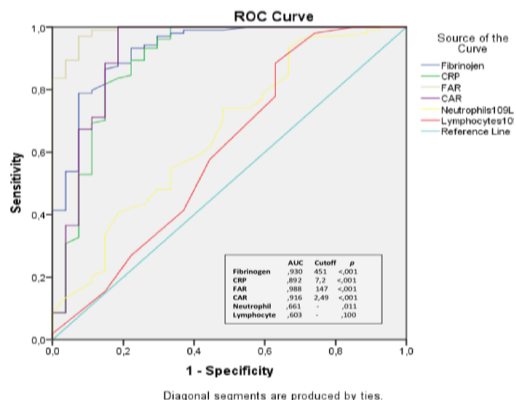
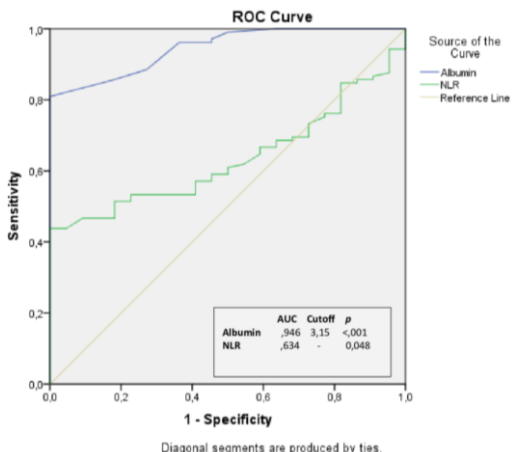


Figure 2: ROC curve analysis for hematological parameters which show direct relationship with AVF maturation



A multiple linear regression analysis was carried out and the outliers were controlled for before proceeding with the logistic regression analysis. Accordingly, the FAR and CAR were excluded from the logistic regression analysis, as they had the highest level of correlation with other parameters. A logistic regression analysis was conducted after the assumptions were met. The dependent variable of the test was taken as “Functional Fistula - 0” and “Dysfunctional Fistula - 1”. Accordingly, the accuracy rate of the prediction was 79.5.

An Omnibus test revealed a significant difference between the two blocks (Block 0 and Block 1) (Chi-square = 121.423, SD = 3, $P<0.001$, $P<\alpha$). Hosmer and Lemeshow tests identified no significant difference between the predicted values and the observed values, with a P -value of 0.998 (Chi-square = 1.028, SD = 8 ($\alpha = 0.05$, $P>\alpha$)). In other words, the model can be suggested to reflect the actual condition.

The Nagelkerke R² value revealed that the independent variables explain 94% of the variation in the “fistula dysfunction” dependent variable. Values greater than 30% are considered acceptable, and thus the model can be suggested as having a high prediction ability.

Table 3 presents the results of a Wald Test, in which a variable with a value of less than 0.05 (or 0.1) is considered significant. Accordingly, the fibrinogen variable was significant, with a value of 5%, while the fibrinogen, albumin and CRP variables were significant with a significance level of 10%.

Table 3: Evaluation of independent variables

	Wald	P-value
Fibrinogen	6.620	0.010*
Albumin	3.639	0.056 [§]
CRP	3.154	0.076 [§]
Constant	0.720	0.396

* $\alpha=0.05$, [§] $\alpha=0.10$

Discussion

Tunneled catheters can save lives in cases where the vascular structures are unsuitable for AVF creation, although autologous AVF is the preferred approach to vascular access for dialysis purposes, as catheter insertion is not superior to AVF when considering the above-stated complications and the long-term patency of vascular access [9].

AVF may seem to be less harmful than a catheter, although there may be some undesired effects due to abnormal blood circulation. According to the results of a systematic review, the most common complications and pathological conditions associated with AVF are venous aneurysms, ischemic steal syndromes, infection, venous and arterial thrombosis, venous hypertension, pulmonary hypertension, hyperdynamic heart failure, and hematoma due to recurrent cannulation [10]. As can be understood from these results, AVF creation is unfortunately not a risk-free approach. There is a lack of data in literature regarding the patency rate of AVFs in the early period, with a wide range of early primary patency rates (between 24 and 92%) reported [11,12], while early dysfunction rates ranging between 5% and 62% have been reported [10].

This wide range of patency rates reported in literature may be explained by the lack of a thorough preoperative examination of the vascular structure by Doppler USG. The fact that both the vein and the artery to be used in fistula creation must have a minimum diameter of 2.0 mm is an important detail that

may be overlooked [13]. Inadequacies in the vascular anatomy may be determined beforehand through an appropriate ultrasonographic examination, and the most suitable interventions may be selected accordingly. In our clinic, not all patients underwent preoperative Doppler USG examinations during the study period, although no radiocephalic fistulas were created in patients deemed to have small caliber cephalic veins at the forearm level upon visual inspection, with the operation being performed at the brachial level in such patients. Even though the surgeon's familiarity with anatomic structures can lead to a correct decision upon inspection, the method may fail due to the lack of quantitative measurements. This can be regarded as a limitation of the present study, in which the early patency rate was 78.5%.

It was anticipated in the present study, which is based on preoperative blood samples, that hematological changes due to additional postoperative pathologies may affect the study outcomes. There have been many studies in literature linking preoperative NLR with the course and outcome of operations [14]. In one study comparing preoperative and postoperative NLR values, the AVF patency rate was higher in patients with high preoperative but low postoperative NLR values, suggesting that low preoperative and postoperative NLR values may indicate early fistula failure [1]. The present study focused only on postoperative NLR values but found NLR values to be lower in patients with early fistula dysfunction, and the difference between the groups was statistically significant. The ROC curve analysis identified higher NLR values in Group 1.

When the parameters constituting the NLR measurement are evaluated separately, both the neutrophil and lymphocyte counts were significantly higher in Group 2 than in Group 1, and the NLR was higher in Group 1, suggesting the lymphocyte count to be more predictive of AVF dysfunction than neutrophil count. The main finding related to lymphocytes is that the count is elevated in the presence of infection, and particularly in viral infections, autoimmune disorders, malignancies and chronic diseases. The unfavorable effect of lymphocytes, as well as the cytokines released from lymphocytes, on the success of surgical procedures may be considered an area of interest in further studies.

CRP levels change in the presence of infections, with high levels decreasing the success of surgical procedures. A common finding of studies in literature is that elevated CRP levels are associated with negative outcomes in various surgical procedures and medical therapies [15,16]. In the present study, CRP was higher in Group 2 than in Group 1. In a ROC curve analysis, high CRP values were recorded in Group 2, with a cut-off value of 7.20 for CRP. The presence of an active infection certainly required the postponement of surgery. Considering the findings of the present study, the postponement of operations is a rational option in patients with high CRP values, being indicative of an active infection, although the patient may be asymptomatic. In this regard, a high CAR – measured based on CRP values – has been shown to be associated with increased mortality and morbidity in literature [16]. In the ROC curve analysis, the patients in Group 2 had a high CAR with a cut-off level of 2.49. The high CAR values in Group 2 were expected, considering the association between high CRP values and increased mortality and morbidity.

Dyslipidemia values were similar in the two groups and showed no statistically significant difference. Despite the proven negative effect of hyperlipidemia on the vascular system, the lack of a significant difference between the groups in the present study in this regard can be attributed to the study design being limited to early postoperative results. A study evaluating AVF stenosis over a period of 5 years revealed LDL to be associated with stenosis [17], indicating an association between LDL and stenosis in the long term, but with no effect on early fistula stenosis.

There have been many studies reporting increases in blood viscosity to be an independent risk factor [18, 19]. Parameters such as dyslipidemia, DM, smoking, hematocrit level, erythrocyte deformability and fibrinogen all affect blood viscosity [20]. In the present study, fibrinogen levels were higher in Group 2 than in Group 1, and the between-group difference was statistically significant. A ROC curve analysis revealed high fibrinogen levels in Group 2 with a cut-off level of 451, which is a finding that is consistent with earlier studies in literature. Avoiding the activation of fibrinogen, which is involved in the thrombosis pathway, through the use of antiaggregant and anticoagulant medications may indirectly increase the success of surgical interventions.

Albumin was selected as the key actor in the present study, in that it constitutes more than half of plasma serum concentration. Blood concentrations of albumin were decreased in malnutrition and infection. Depending on the plasma concentrations, albumin possesses antiaggregant, anticoagulant, anti-inflammatory and anti-oxidant properties, based on its osmotic effect [21]. Low albumin levels are known to cause cardiovascular diseases, ischemic stroke, and venous thromboembolism [22]. Considering its functions and key effects, it comes as no surprise that changes in albumin values significantly affect prognosis. In the present study, albumin values were significantly lower in Group 2. A ROC curve analysis showed a cut-off value of 3.15 for albumin, and the values were significantly lower in Group 2. Furthermore, the results of a logistic regression analysis suggested that low albumin levels can be regarded as a cause of early AFV dysfunction. Studies have suggested that patients without malnutrition or high blood protein and albumin levels are resistant to vascular access failure, which is consistent with the findings of the present study [23]. Similarly, high FAR values were found in Group 2, with a cut-off value of 147.

Limitation

The limitations of this study include its retrospective and single-center design, and small sample size. AVF maturation and patency rates may be better predicted through an examination of the parameters that provide more details of blood viscosity.

Conclusion

NLR has been the subject of many studies, but since we are unable to influence them, how useful it is to know these values is debatable. The present study has shown albumin levels to affect AVF maturation, and low albumin levels are associated with an increased risk of AVF dysfunction. Blood albumin levels can easily be increased with proper nutrition and intravenous replacement, and more AV fistula patency rates can be gained, which gives us the chance to influence the AVF maturation process, unlike with NLR.

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