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Study Of Clinical and Biochemical Factors Affecting Early Failure of Arteriovenous Fistula in a Tertiary Care Hospital of Bangladesh

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Abstract

Background: Arteriovenous fistula is necessary for the maintenance of hemodialysis patients. Arteriovenous fistula patency is mandatory for adequate dialysis. However, early arteriovenous fistula failure is a substantial burden that influences the morbidity and mortality of maintenance hemodialysis patients. Clinical factors (BMI, BP, and DM) and biochemical factors (S. CRP, S. albumin, S. ferritin, fibrinogen, and NLR) are associated with early arteriovenous fistula failure.

Aims of the study: To determine and explore the clinical and biochemical factors affecting early failure of arteriovenous fistula.

Materials and methods: This observational study was conducted from January 2019 to July 2020 in the Department of Nephrology, Dhaka Medical College Hospital. Eighty-two patients with CKD stage 5 and ESRD were included in this study according to inclusion and exclusion criteria. Body mass index, blood pressure, serum hs C-reactive protein, serum albumin, serum ferritin, fibrinogen, and Neutrophil lymphocyte ratio were measured. After that, AVF construction was done. After AVF construction, participants were followed up weekly. During follow-up, a clinical examination (inspection, palpation, and auscultation) of AVF was performed to evaluate AVF status. AVF was grouped into AVF failure and AVF functioning. Data was analyzed by SPSS version 25.

Results: The mean age of the patient was 47.13±13.48 years in the AVF failure group and 45.31±10.78 years in the AVF functioning group. High BMI (24.66 ±3.17 kg/m2) (P=0.002), DM (P=0.015), smoking (P=0.043), and diastolic blood pressure (63.7± 12.72 mm hg) (P=0.001) had a significant association with early AVF failure. Biochemical factors such as high hs CRP (36.5±27.03mg/l) (P=0.001), low albumin (28.04±7.05 g/l) (P=0.001) high ferritin (711.46±419.94 micg/l) (P=.001), high fibrinogen (507.47±178.45 mg/dl) and (P=0.001) NLR (6.36±2.31) (P=.001) were significantly associated with early AVF failure. However, no significant association was found between age and sex with early AVF failure. A multivariate logistic regression model found that BMI, smoking, DBP, hs CRP, and fibrinogen were independent predictors of early AVF failure.

Conclusions: High body mass index, smoking, comparative low diastolic blood pressure, high hs C- reactive protein, and high fibrinogen were independent predictors of early arteriovenous fistula failure.

Keywords: Tidal Peritoneal Dialysis; Pregnancy; Chronic Kidney Disease.

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Introduction

For advanced health facilities in recent years, the longevity of CKD and ESRD patients has been increasing [1]. The prevalence of ESRD patients is growing by around 7-9% every year [2]. Due to the gradual growth of ESRD patients throughoutthe world, thedemand for renalreplacementtherapy is increasing. Vascular access is mandatory for maintenance hemodialysis [2]. Arteriovenous fistula (AVF) is a connection between an artery and a native vein, the most critical vascular access [3]. The preferred site of AVF construction is in the non-dominant distal forearm (brachiocephalic), and the early failure rate varies from 5% to 41%. A proximal site or upper arm may be used for AVF creation, and the early failure rate varies from 2% to 26% [4]. At the clinical level, early AVF failure has been defined as never developing adequately for hemodialysis (failure to mature) or failing within one month of starting hemodialysis [2]. For AVF, maturation usually takes 6 to 10 weeks. Late AVF failure is defined as a failure that occurs after three months of successful use [4]. AVF complications are significant precursors of mortality and morbidity in hemodialysis patients [3]. AVF failure also imposes a substantial financial burden [5]. AVF complications are infection, bleeding, thrombosis, stenosis, aneurysm, pseudoaneurysm, steals syndrome, carpal tunnel syndrome, nerve injury, distal ischemia necrosis etc. [4]. Venous stenosis and the presence of accessory veins are the two leading causes of early failure. Factors associated with early AVF failure are demographic, clinical, hematological, and biochemical. Demographic and clinical risk factors are older age, female gender, smoking, obesity, diabetes mellitus, hemodynamic profile derangement (hypotension, low DBP and low MAP), and vascular diseases [6]. Biochemical factors (especially inflammatory markers) associated with early AVF failure are increased C reactive protein (CRP), low serum albumin, high ferritin, high fibrinogen, etc. [6- 9]. Hematological factors include increased neutrophil-lymphocyte ratio (NLR), low hemoglobin, and high ESR [10]. Older age is associated with atherosclerosis, which may cause early AVF failure [11]. The female gender is at a high risk of developing early AVF failure due to low-caliber blood vessels and may fail to dilate [12]. Smoking may cause atherosclerosis and peripheral vascular disease, which may play a role in early AVF failure [13]. Obesity and DM lead to metabolic changes that may be associated with inflammation, which plays a role in AVF failure [9,14]. Low blood pressure causes a low flow state in the AVF, and it has been postulated that this may put forward the formation of thrombosis in the AVF, ultimately resulting in early AVF failure [15]. Anemia in ESRD patients with diabetes is associated with ESA resistance, inflammation states, and the presence of multiple comorbidities like cardiovascular disease [16]. Thus, diabetes and low hemoglobin play a role in early AVF failure [2]. CRP is a primary acute phase reactant, which varies widely according to the grade of inflammation, infection, and tissue damage [17]. High CRP is a strong positive predictor for AVF thrombosis and stenosis, independent risk factors for early AVF failure [18]. Albumin synthesis is decreased in uremia due to continuous inflammation, insufficient protein, calorie intake, increased catabolic status, etc. [19]. Serum albumin maintains the oncotic pressure. Different levels of serum albumin represent different pathophysiological conditions (dehydration, malnutrition, poor tissue healing, and oedema) that can consequently affect the wound healing process, inflammation, and arteriovenous fistula flow rate, ultimately leading to develop early AVF failure [20]. Fibrinogen is also an acute-phase reactant. High fibrinogen levels cause blood coagulation, platelet aggregation, and vascular wall changes [7]. High fibrinogen level is an independent risk factor for cardiovascular disease and early AVF failure [21]. Ferritin is another marker of inflammation that may be associated with early AVF failure [22]. In systemic inflammatory response, circulating components of complete blood count are changed, namely neutrophils and lymphocytes. Neutrophilia is associated with relative lymphocytopenia [23]. High NLR reflects inflammation and, thus, is related to early AVF failure [24]. Risk factors should be assessed to prevent early AVF failure, and further measures may be taken to modify/correct or treat as possible. In this study, we tried to determine, explore, and find out the relationship between early AVF failure and affecting factors such as demographic, clinical (age, sex, body mass index, smoking, blood pressure, diabetes mellitus), biochemical (C-reactive protein, albumin, ferritin, and fibrinogen) and neutrophil-lymphocyte ratio. The study aims to identify the clinical and biochemical factors affecting early failure of arteriovenous fistula.

Methodology & Materials

This was an observational study. All patients with CKD 5 and ESRD were assessed accordingly and attended indoors and outdoors in the Department of Nephrology, Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh. After selecting participants according to the inclusion and exclusion criteria, they were approached for inclusion in the study. A total of eighty-two patients with CKD stage 5 and ESRD who require AVF construction were included in this study from January 2019 to July 2020. History-taking focused on clinical features, and a physical examination was done. All peripheral pulses were scrutinized. Ethical approval was taken from DMC's Ethical Review Committee (ERC). Following the information about the study's aim, objectives, and procedure, informed written consent was obtained from each participant.

Inclusion criteria:

- Age more than 18 years.

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- CKD Stage 5 and ESRD patients who require AVF construction.

Exclusion criteria:

- Active infection.
- Diagnosed case of CLD.
- History of previous AVF failure.
- Pregnancy.

Investigations including CBC, S. hs CRP, S. Albumin, S. Ferritin, and Fibrinogen were done. For these investigations, 8-10 ml of blood was collected through venipuncture from the antecubital site using an aseptic method. For the serum hs CRP, ferritin, and albumin test, 3 ml of blood was taken within the sample clotted activator tube, then 10 minutes kept in the rack, centrifuged with 3500 rotation per minute (RMP) for 15 minutes. After getting all the required reports, they were referred to the Department of Urology and Vascular Surgery of DMCH for AVF construction. After the AVF construction, patients were followed up with a clinical examination of AVF (inspection, palpation, and auscultation) every 7 to 10 days.

If any complication (sign of infection, bleeding, hematoma, sign of AVF failure) or any features prone to AVF failure were observed for further management, they were consulted with respective surgeons (department) and assesed accordingly. Particularly in the sixth and tenth week of AVF construction, participants were followed up. During follow-up, participants were examined thoroughly, and special attention was paid to AVF, including inspection, palpation (thrill), auscultation(bruit), pulse augmentation test, and arm elevation test for clinical evaluation of AVF status. AVF status was either failure or functioning. Then, data was enrolled in either AVF failure or AVF functioning groups. Finally, participant's age, sex, smoking history, BMI, DM, S. hs CRP, S. Ferritin, S. Fibrinogen, S. Albumin, and NLR with early AVF failure were analysed.

Operational definitions:

Early failure of arteriovenous fistula (AVF):

Early arteriovenous fistula failure has been defined as an arteriovenous fistula that never develops adequately for dialysis (failure to mature) or fails within one month of starting dialysis [2]. Clinically early AVF failure is characterized by

1) absence of continuous thrill on palpation,

2) absence of continuous bruit on auscultation,

3) absence of venous dilation or engorgement,

4) less than six cm length of straight segment of fistula,

5) poor augmentation of pulse-on-pulse augmentation test

6) absence of collapsing of superficial vein on arm elevation test

7) absent or feeble pulse or absence of soft compressible pulse

8) low blood flow at initial dialysis and

9) signs of inflammation [4,5].

Arteriovenous fistula:

Abnormal connection of artery and vein, either congenital or surgically created. Dialysis arteriovenous fistula is defined as a surgically created connection between artery and vein in the limb of the patients who need to undergo hemodialysis, a process in which blood is removed from the body, cleansed, and then return to the body. The fistula causes the vein to become enlarged and allows blood to be easily withdrawn and replaced during dialysis.

Data collection:

A questionnaire was prepared considering key variables like demographic data, clinical presentation, clinical findings, and investigations, which were collected, verified by the guide, and collected by the researcher. After the selection of the patient, the aims, objectives, and procedures of the study were explained in understandable language to the patient. Risks and benefits were also made clear to the patient. The patients were encouraged to participate and allowed to withdraw from the study. Then, informed written consent was taken from each patient.

Statistical analysis:

Statistical analysis was done using the Statistical Package for Social Sciences version 25.0 for Windows (SPSS Incl., Chicago, Illinois, USA). Continuous variables were expressed as mean±SD and categorical variables as frequencies and proportions. The relationship between independent and dependent variables was analyzed using the Chi-square test, logistic regression test, and unpaired t-test. Statistical significance was assumed when the probability value was less than 0.05.

Result

Table 1 shows the distribution of the study patients by baseline characteristics. It was observed that the mean age was 47.13±13.48 years in the AVF failure group and 45.31±10.78 years in the AVF functioning group. Almost half of the patients were female in the AVF failure group, and 25(42.4%) were in the AVF functioning group. The mean BMI was 24.66±3.17 kg/m2 in the AVF failure group and 22.07±3.43 kg/m2 in the AVF functioning group. More than half (56.5%) of the patients had a smoking history in the AVF failure group and 19(32.2%) in the AVF functioning group. Almost three-fourths (73.9%) of the patients had DM in the AVF failure group and 26(44.1%) in the AVF functioning

group. The mean SBP was 134.13±21.3 (mm Hg) in the AVF failure group and 147.51±15.77 (mm Hg) in the AVF functioning group. The mean DBP was 63.7±12.72 (mm Hg) in the AVF failure group and 80.81±14.61 (mm Hg) in the AVF functioning group. The mean MAP was 87.17±11.6 (mm Hg) in the AVF failure group and 102.51±13.26 (mm Hg) in the AVF functioning group. The mean creatinine was 7.91±1.7(mg/dl) in the AVF failure group and 7.94±1.43(mg/dl) in the AVF functioning group. Most (82.6%) of patients had distal AVF in the AVF failure group and 49(83.1%) in the AVF functioning group. The differences between the two groups were statistically significant in BMI, smoking, DM, SBP, DBP, and MAP ($p<0.05$). Table 2 shows the distribution of the study patients by clinical and risk factors profile. It was observed that nearly half of 10 (43.5%) of the patients belonged to BMI 23.0-27.5 kg/m2 (overweight) in the AVF failure group and 11(18.6%) in the AVF functioning group. Almost three-fourths (73.9%) of the patients had DM in the AVF failure group and 26(44.1%) in the AVF functioning group. More than half (56.5%) of the patients had a smoking history in the AVF failure group and 19(32.2%) in the AVF functioning group. The difference in BMI, DM, and smoking was statistically significant ($p<0.05$) between the two groups. Table 3 shows the distribution of the study population by biochemical variables (absolute value). The mean hs CRP was 36.5±27.03 mg/l in the AVF failure group and 9.31±8.52 mg/l in the AVF functioning group. The mean S. Albumin was 28.04±7.05 g/l in the AVF failure group and 33.85±5.24 g/l in the AVF functioning group. The mean S. Ferritin was 711.46±419.94 micg/l in the AVF failure group and 374.82±328.78 micg/l in the AVF functioning group. The mean fibrinogen was 507.47±178.45 mg/dl in the AVF failure group and 293.32±107.1 mg/dl in the AVF functioning group. The mean NLR was 6.36±2.31in the AVF failure group and 2.97±1.26 in the AVF functioning group. The difference between the two groups was statistically significant ($p<0.05$). In multivariate logistic regression model analysis, it was found that BMI had 1.014 times (95.0% C.I. 0.948 to 1.085 times) more significantly associated with AVF failure. Smoking was 1.039 times (95.0% C.I. 0.998 to 1.082 times) and was more associated considerably with AVF failure. DBP had 1.060 times (95.0% C.I. 1.004 to 1.120 times) more associated considerably with AVF failure. However, age, gender, DM, and SBP were not significantly associated with AVF failure. So, High BMI, smoking, and low DBP were independent predictors for early AVF failure (Table 4). In multivariate logistic regression analysis, CRP had 1.080 times (95.0% C.I. 0.921 to 1.265 times) more significantly associated with AVF failure. Fibrinogen had 1.092 times (95.0% C.I. 0.983 to 1.413 times) more associated considerably with AVF failure. However, albumin, ferritin, and NLR were not significantly associated with AVF failure. So, hs CRP and fibrinogen were independent predictors of early AVF failure (Table 5). Table 6 shows that among 82 participants, in the sixth week, 21 participants had AVF failure. In the 10th week, among 61 functioning AVFs, only 2 participants had AVF failure. In the 6th and 10th weeks, 23(28%) participants had AVF failure, and 59 (72%) had functioning AVF.

Table 1: Distribution of the study patients by baseline characteristics (n=82).

Baseline characteristics	AVF Failure (n=23)		AVF Functioning (n=59)	
	n	%	n	%
Age (years) Mean ± SD	47.13±13.48		45.31±10.78	
Gender				
Male	12	52.2	34	57.6
Female	11	47.8	25	42.4
BMI (kg/m2)				
Mean ± SD	24.66±3.17		22.07±3.43	
Smoking history	13	56.5	19	32.2
Presence of DM	17	73.9	26	44.1
SBP (mm hg) Mean ± SD	134.13±21.3		147.51±15.77	
DBP (mm hg) Mean ± SD	63.7±12.72		80.81±14.61	
MAP (mm hg) Mean ± SD	87.17±11.6		102.51±13.26	
S. Creatinine (mg/dl)	7.91±1.7		7.94±1.43	
Sites of AVF				
Distal	19	82.6	49	83.1
Proximal	4	17.4	10	16.9

Table 2: Distribution of the study patients by clinical and risk factors profile (n=82).

Clinical variables	AVF Failure (n=23)		AVF Functioning (n=59)		P value
	n	%	n	%	
BMI (kg/m2)					
<18.5	2	8.7	15	25.4	0.008s
18.5-22.9	4	17.4	25	42.4	
23.0-27.5	10	43.5	11	18.6	
>27.5	7	30.4	8	13.6	
Presence of DM					
Yes	17	73.9	26	44.1	0.015s
No	6	26.1	33	55.9	
Smoking history					
Yes	13	56.5	19	32.2	0.043s
No	10	43.5	40	67.8	

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Table 3: Distribution of the study patients by biochemical variables (absolute value) (n=82).

Biochemical variables	AVF Failure (n=23)	AVF Functioning (n=59)	P value
	Mean ± SD	Mean ± SD	
S. hs CRP (mg/l)	36.5±27.03	9.31±8.52	0.001s
S. Albumin (g/l)	28.04±7.05	33.85±5.24	0.001s
S. Ferritin (micg/l)	711.46±419.94	374.82±328.78	0.001s
Fibrinogen (mg/dl)	507.47±178.45	293.32±107.1	0.001s
NLR	6.36±2.31	2.97±1.26	0.001s

Table 4: Association of demographic, risk, and clinical factors related to AVF failure (n=82).

Characteristics	B	S.E.	P value	OR	95% C.I.	
					Lower	Upper
Age	0.014	0.034	0.681ns	0.78	0.633	0.96
Gender	1.331	1.001	0.184ns	0.264	0.037	1.88
DM	0.974	0.84	0.246ns	0.378	0.073	1.959
BMI	0.249	0.106	0.019s	1.014	0.948	1.085
Smoking	2.526	1.029	0.014s	1.039	0.998	1.082
SBP	0.039	0.021	0.063ns	0.08	0.011	0.601
DBP	0.059	0.028	0.036s	1.06	1.004	1.12

Table 5: Association of biochemical factors (inflammatory markers) related to AVF failure (n=82).

Characteristics	B	S.E.	P value	OR	95% C.I.	
					Lower	Upper
S. hs CRP	0.073	0.035	0.037s	1.08	0.921	1.265
S. Albumin	0.077	0.081	0.344ns	0.93	0.868	0.996
Fibrinogen	0.008	0.005	0.043s	1.092	0.983	1.413
S. Ferritin	0.001	0.001	0.271ns	0.999	0.996	1.001
NLR	0.435	0.233	0.062ns	0.647	0.41	1.021

Table 6: Distribution of participants according to AVF condition and time of AVF Failure (n=82).

Duration	AVF status	
	AVF failure (N)	AVF Functioning (N)
In the 6th weeks	21	61
In the 10th weeks	2	59
Total (6th+10th) week	23	59

Discussion

Chronic kidney disease is a public health problem whose prevalence is increasing [25]. Among hemodialysis patients, arteriovenous fistula use is also increasing [12,26]. Functioning AVF is mandatory for maintenance hemodialysis [1]. This observational study was conducted to identify, explore, and estimate the clinical and biochemical factors associated with early AVF failure. This study found that the participants' mean age was 47.13 ± 13.48 years in the AVF failure group and 45.31± 10.78 years in the AVF functioning group. The association between age and early AVF failure was insignificant (P = 0.525). Khavanin Zadeh M et al. (2015) found that the mean age was 53.27±17.47 years; on the other hand [1], Lok CE et al. (2006) found that patients over 65 years had early AVF failure rate double that of younger patients [11]. There was no significant difference between male and female with AVF failure. Similarly, Kaygin, MA et al. (2013) found no significant difference between males and females with early AVF failure [7]. Pandey, S et al. (2019) found that the early AVF failure rate of females (33.3%) was higher than that of males (24.6%) and was insignificant, which was not similar to this study [27]. Female gender was associated with a high rate of early AVF failure, which may be due to veins in women being less likely to dilate and low caliber vessels [12].

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In this study, 28% (23) had early AVF failure. Similarly, some studies found that the early AVF failure rate was 21.2 %, 23%, 30.6%, and 27.7 in their study [27-30]. Smoking was significantly associated with early AVF failure, which was similar to another study. Ozdemir et al. (2007) and Wetzig et al. (1985) found the association between smoking and early AVF failure in their study [13,31]. This study showed that high BMI was significantly associated with early AVF failure. Mean BMI was 24.66±3.17 (kg/m2) and 22.07±3.43 (kg/m2) in the AVF failure and functioning groups, respectively. Kaygin, MA et al. (2013) found that BMI was 22.6±4.2 (kg/m2) and 21.9 ± 46 (kg/m2) m2) in the AVF failure and functioning groups, respectively [7]. Segal et al. (2003) also found that high BMI was associated with early AVF failure, similar to this study [32]. This study also found that comparatively low DBP and MAP were associated with early AVF failure. Pandey S et al. (2019) found that low diastolic and mean arterial blood pressures were significantly associated with early AVF failure, similar to this study [27]. Low DBP was a risk for early AVF failure due to the formation of thrombosis in AVF [33]. In this study, serum high hs CRP was significantly associated with early AVF failure. The mean C-Reactive protein was 36.5±27.03 mg/l and 9.31±8.52 mg/l in the AVF failure and functioning groups, respectively. The study of Kaygin, MA et al. (2013) found high CRP 18.6±4.3 mg/l and 4.6±2.2 mg/l, respectively, in AVF failure and AVF functioning groups [7]. In 2015, Khavanin ZM et al. found that high hs CRP was associated with early AVF failure, similar to this study [34]. This study also found a significant association between lower S. albumin and early AVF failure. In this study, the mean S. albumin was 28.04±7.05 g/l in the early AVF failure group and 33.85±5.24 g/l in the AVF functioning group. Similarly, the study by Tanaka A et al. (2016) found that S. Albumin was significantly lower (2.7±0.8 g/dl) in the early AVF failure group than in the functional AVF group (3.0±0.6 g/dl) [35]. In another study, Kordzadeh A. et al. (2017) also found that patients with an S. Albumin level equal to or above 35 gm/l had a 60% lower chance of fistula failure, similar to this study [36]. In this study, high S. Ferritin was associated with early AVF failure. Afsar B. (2013) found that high ferritin was associated with early AVF failure, similar to this study [22]. This study found the association between high fibrinogen and early AVF failure was significant. Kaygin MA et al. (2013) showed that fibrinogen level was high in 29.5% of functioning AVF cases and 81.3% of early failure AVF cases, similar to that study [7]. The association between NLR and early AVF failure was significant in this study. Usman et al. (2017) found that high NLR predicted early AVF failure [24]. In a logistic regression model, Yilmaz et al. (2014) advocated that NLR was associated with early AVF failure, similar to this study [38]. NLR is a simple parameter that positively correlates with levels of other inflammatory markers that reflect systemic inflammation [39-41]. In this study, it was found that age and sex had no influence on developing early AVF failure, but smoking, high BMI, DM, comparative low blood pressure (DBP MAP), low serum albumin, high serum hs CRP, high serum ferritin, high serum fibrinogen, and raised NLR were associated with early arteriovenous fistula failure. In multivariate logistic regression analysis of age, sex, BMI, DM, smoking, SBP, and DBP status, effects on failure of AVF were evaluated; BMI, smoking, and comparative low DBP were significantly associated with early AVF failure. Also, multivariate logistic regression analysis among the inflammatory markers (hs CRP, albumin, fibrinogen, ferritin, and NLR) status effect on AVF failure was evaluated; high hs CRP and high fibrinogen were significantly associated with early AVF failure. Multivariate logistic regression found that high BMI, smoking, comparative low diastolic blood pressure, high CRP, and high fibrinogen were strongly associated with early AVF failure.

Limitations of the study: The study has several limitations. The sample size is relatively small, with only 82 participants, which may limit the generalizability of the findings. The study is observational. Thus, causal relationships cannot be established. There is potential selection bias, as patients were recruited from a single tertiary care hospital, which may not represent the broader population. The follow-up period was also limited to 10 weeks, potentially overlooking late AVF failures. Furthermore, the study relies on self-reported data for variables such as smoking and BMI, which may introduce recall bias or inaccuracies.

Conclusion and Recommendations

This study identifies critical clinical and biochemical factors influencing early arteriovenous fistula (AVF) failure in hemodialysis patients. Significant associations were found between early AVF failure and clinical factors such as high BMI, smoking, and low diastolic blood pressure. Biochemical markers, including elevated C-reactive protein (CRP) and fibrinogen levels, were also strongly linked to early failure. Multivariate logistic regression analysis confirmed these associations, underscoring the importance of these factors in predicting early AVF failure. These findings suggest that addressing modifiable risk factors such as BMI and smoking, alongside monitoring inflammatory markers, could improve AVF outcomes in clinical practice.

Conflict of interest: None declared.

Ethical Approval

The study was approved by the Institutional Ethics Committee.

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