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A Pilot Study to Identify Haematological Markers in the Failure of Arterio-Venous Fistulas for Haemodialysis in End Stage Renal Disease

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Abstract

Introduction: Arterio Venous Fistulas (AVFs) may be radio-cephalic, brachiocephalic or brachiobasilic, however a radio-cephalic access is preferred for patients with end stage renal disease requiring haemodialysis. After their creation, the minimum time for AVF maturation is around two months. Primary AVF failure is defined as an AV fistula that is never usable or fails within the first three months of its use. There are several observations that indicate the role of inflammation in failure of AVF. Elevated CRP has been observed to be associated with early fistula failure and our study purported to correlate the same.

Methodology: In this pilot study, 50 patients of end stage renal disease (ESRD) over 18 years of age, after fulfilling inclusion and exclusion criteria, underwent the creation of a radio-cephalic AVF. All patients had pre-operative values of CRP, haemoglobin and albumin estimated, which were repeated again on post-operative day 2. All patients were followed for three months to assess for primary failure of fistula.

Results: Out of the 50 patients included in the study, six patients were lost to follow up. The mean age of the patients was 41.48 ±13.46 years. 31.8% (14 patients) developed primary failure of the AVF. No significant correlation was identified between primary failure of AVF and the pre-operative hemoglobin and albumin levels. While a pre-operative CRP level<1 mg/dl did not show a significant correlation with failure of AVF, 71.4% of failed fistulas showed CRP levels> 5.4 mg/dl (p=0.025, Sn: 71.43%, Sp: 66.7%). Number of dialysis per week through other sites, and comorbidities like hypertension and diabetes mellitus did not show any significant association with primary failure of AVF.

Conclusion: Pre-operative CRP levels>5.4 mg/dl can predict the primary failure of AVF with a sensitivity of 71.43% and specificity of 66.7%. However further studies are required to validate the same.

Keywords

End Stage Renal Disease (ESRD); Renal replacement therapy; Arterio venous fistula; Neointimal hyperplasia; C - reactive protein

Introduction

End Stage Renal Disease (ESRD) patients require lifelong renal replacement therapy. Renal replacement therapy may be permanent in the form of renal transplant or a temporary modality like dialysis. Haemodialysis is regarded as the best modality of renal replacement therapy until the patient undergoes renal transplant. Successful haemodialysis requires an ideal vascular access like AVF, CVC (Central Venous Catheter) or an AVG (Arterio Venous Graft). Arterio Venous Fistula (AVF) is the preferred vascular access for haemodialysis (HD) in chronic kidney disease patients and is considered as gold standard. It is economical, durable and associated with less complications like infections and thrombosis. Other important benefits being its permanent nature as it may last for many years. AVF is always beneath the skin that protects it from infections and provides greater blood flow for better treatment. Brasica Cimino fistulas are currently accepted as the best mode of vascular access for haemodialysis (HD) [1]. According to National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) Clinical Practice Guidelines, and the 2008 Society for Vascular Surgery guidelines, the order of preference for the creation of AV fistula is radio-cephalic, brachio-cephalic, and than brachio-basilic transposition [2,3].

After their creation, the minimum time for AV fistula maturation is six to eight weeks [4]. Primary AV fistula failure is defined as an AV fistula that is never usable or fails within the first three months of its use [5]. Various demographic and patient related factors (clinical and radiological) have influence on success and maturation of AVFs. As efforts have intensified to preferentially create AV fistulas, the incidence of primary failure has increased, ranging from 20 to 60 percent [6]. The mechanism of such a high failure rate among any elective surgery is little known and the reasons for this is quite variable in literature. There is dearth in literature regarding the rate of fistula maturation and factors attributing to it, however

various risk factors attributing to failure of AV fistula are obesity, older age, female gender, ethnicity other than caucasian, cardiovascular disease, peripheral vascular disease, diabetes, thrombophilia and surgeon experience [7,8].

Neointimal hyperplasia (NIH) due to persistent inflammation in patients of ESRD has been associated with failure of AVFs [9,10]. Elevated CRP, an inflammatory marker, has been observed to be associated with early fistula failure and our study purported to correlate the same.

Materials and Methods

The subjects for this prospective pilot study were patients of ESRD referred to the Department of Surgical Disciplines, AIIMS for AVF creation. The surgery was performed in a single surgical unit. Patients with end stage renal disease were included in the study. A written informed consent was taken from the patients and ICMR/GCP guidelines were followed. All patients over 18 years of age with no previous fistula creation were recruited, history and comorbidities noted, and were subjected to ipsilateral upper limb USG doppler to assess the size of the artery and vein with size<2 mm excluded. Blood samples were collected within 2 days of the planned AVF creation, for estimation of CRP, hemoglobin and albumin levels. Between October 2018 and May 2019, a total of 50 patients underwent radio-cephalic AVF creation, out of which 6 patients were lost to follow up. The average age of the patients was 41.48 ± 13.46 years. Of the remaining 44 patients, 27 were males (61.36%) and 17 were females. The patients were followed up for a period of three months as shown in **Table 1.** Blood for CRP levels was collected in a serum vial and analysed by an automated Beckman Coulter AU480 clinical chemistry analyser which can detect levels upto 0.2 mg/L of CRP in serum/plasma [10].

Inclusion criteria

- Patients included in the study were:
- CKD stage V (ESRD)
- Age above 18 years
- No previous history of AVF creation
- Patients undergoing radio-cephalic AVF surgery
- Cephalic vein diameter of >2mm at wrist on USG doppler

Exclusion criteria

- Age less than 18 years
- Previous history of AVF surgery (Failed / non functional AVF)
- Patient refusal for consent
- Cephalic vein diameter <2mm at wrist
- Fistulas other than radio-cephalic (brachio-cephalic, brachio-basilic AVFs)

Statistical analysis

Data is reported as mean ± SD, median or percentages as appropriate. The association between CRP levels, hemoglobin, albumin, frequency of dialysis and other comorbidities and primary failure of AVFs was analysed. Receiver -operating characteristic (ROC) curves were configured to establish the levels of CRP that predicted the failure of fistula optimally. All analysis was carried out using STATA version 14.0

Results

Between October 2018 and May 2019, a total of 50 patients underwent radio-cephalic AVF creation, out of which 6 patients were lost to follow up. The average age of the patients was 41.48 ± 13.46 years. Of the remaining 44 patients, 27 were males (61.36%) and 17 were females. 14 patients (31.8%; 10 males and 4 females) developed failure to achieve maturation of fistula during the follow up period of three months as shown in **Table 1.** No significant correlation was observed between the failure of AVF and the demographic features.

Table 1: Demographic features.

Variables	Total n=44	Working n=30	Failed n=14
Age	41.48 ± 13.46	43.17 ± 12.03	37.86 ± 15.99
Males	28	18	10
Females	16	12	4

With a CRP cut off of 1 mg/dl, there was no significance between CRP levels and failure of AVF. With a CRP level>5.4 mg/dl, a significance was noted between CRP levels and failure of AVF (P=0.025), with 71.4% of failed AVFs showing CRP levels over 5.4 mg/dl **(Table 2).**

Table 2: CRP level correlation.

Variables	Total n=44	Working n=30	Failed n=14	P value
Pre AVF	13.19 ± 27.79 Median : 4.65	7.51 ± 15.16 Median : 3.3	25.36 ± 42.52 Median : 6.44	0.004
Post AVF	13.82 ± 26.88 Median : 6	5.29 ± 4.97 Median : 3.9	32.08 ± 42.53 Median : 12.5	0.0015
CRP < 5.4	24	20	4	0.025
CRP > 5.4	20	10	10 (71.4%)	

Based on the Receiver-Operator Characteristic curve, it can be deduced that a pre-operative CRP value of 5.4 or more has a Sensitivity of 71.43% and Specificity of 66.7% to predict the failure of the Arterio-Venous Fistula. (P=0.025) **(Figure 1).**

Based on the Receiver-Operator Characteristic curve **(Figure 1)** as above, it can be deduced that a pre-operative CRP value of 5.4 or more has a Sensitivity of 71.43% and Specificity of 66.7% to predict the failure of the Arterio-Venous Fistula (P=0.025).

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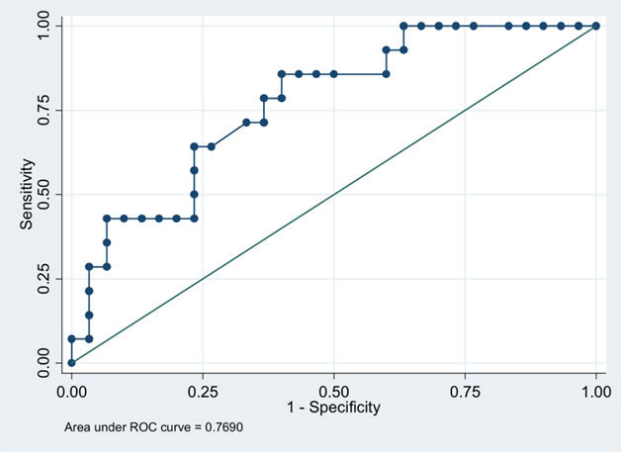

Figure 1: Receiver operator characteristic curve.

Tables 3, 4 and 5 show the correlation between haemoglobin and albumin levels, comorbidities and frequency of dialysis with AVF failure; no statistically significant association was observed between any of the parameters.

Table 3: Correlation with hemoglobin and albumin.

Variables	Total n=44	Working n=30	Failed n=14	P value
Hemoglobin	8.98 ± 1.56	9.19 ± 1.53	8.54 ± 1.59	0.695
Albumin	3.59 ± 0.51	3.58 ± 0.54	3.61 ± 0.55	0.287

Table 4: Correlation with comorbidities.

Co-morbidity	Total	Working	Failed	P value
Hypertension	40	29	11	0.08
Diabetes mellitus	11	7	4	0.72
Coronary artery disease	Nil	NA	NA	
Peripheral vascular disease	Nil	NA	NA	

Table 5: Correlation with frequency of dialysis.

No of dialysis per week	Total n=44	Working n=30	Failed n=14
1/week	8	5	3
2/week	29	21	8
3/week	7	4	3

Discussion

AVFs which are formed by the direct anastomosis of a native artery and vein is an ideal vascular access and very important for the success of hemodialysis. This in turn affects the survival of patients of ESRD. A crucial aspect in identifying the causes of failure of an AVF, has been the discovery of the role of inflammation leading to neointimal hyperplasia (NIH) of these vessels. NIH is an inflammatory process characterised by proliferation of smooth muscle cells and myofibroblasts leading to stenosis of the vessels, thereby increasing the risk of thrombosis. A review by Satish et al. showed the role of neointimal hyperplasia in the failure of AVF. They also observed that patients of ESRD are in a state of persistent inflammation owing to the multiple coexisting comorbid conditions like hypertension and diabetes mellitus, uremic inflammation and increased production and decreased clearance of pro-inflammatory markers [9-11].

CRP, a positive acute phase reactant and a marker of inflammation, was first discovered in the serum of patients during acute phase of pneumococcal pneumonia. It has both pro-inflammatory and anti-inflammatory effects [12,13]. A retrospective study by Kaygin et al. observed the high levels of CRP in patients of failed AVF. They also noted that albumin being a negative acute phase reactant decreased with the level of inflammation in patients of ESRD [14].

Liu et al. investigated and found that inflammatory markers like high sensitivity C-reactive protein (hs-CRP), tissue necrosis factor (TNF), etc were raised in patients with AVF dysfunction [15]. In another study, Afasr et al. observed that Ferretin, hs-CRP, TLC, RDW, neutrophil count, diabetes mellitus were associated with primary AVF failure [16]. Another recent study by Zadeh et al. showed that patients with primary AVF failure had detectable levels of CRP [17]. Given this background, our current study aimed to investigate the correlation of CRP, hemoglobin, albumin levels, and frequency of dialysis and other co morbid conditions of the patient to primary AVF failure.

In our study, the fistula success rate was 68.18% without any post operative radiological or surgical intervention. In some studies USG Doppler parameters like radial artery diameter>2mm and higher flow rates are associated with successful fistula maturation. Very few studies have correlated the outcome of an AVF with proinflamatory cytokines and neointimal hyperplasia. Our data showed that higher CRP levels at the time of fistula creation were associated with an increased risk of primary failure of the AVF. We however found no statistical correlation between fistula failure and levels of hemoglobin and albumin, frequency of dialysis and other comorbidities.

Chou et al. observed that CRP level>0.8 mg/dl predicted not only cardiovascular disease but also the development of vascular access thrombosis with sensitivity of 80.4% and specificity of 72.7% in chronic haemodialysis patients [18].

Another study by Stirbu et al. showed that increasing age [61.3 yrs vs. 58.2 years; p=0.05] and higher CRP levels [1.2 mg/dl vs. 0.5 mg/dl; p=0.0005] were associated with greater risk of secondary fistula failure (but not primary failure) at a median 26 months. They also noticed that pre-emptive fistula (created prior to starting HD) had a lower failure rate [10].

Despite the high rates of AVF failure and the associated burden on healthcare expenditure, the descriptions of determinants of loss of AVF patency are insufficient. While our study has shown that a marker of inflammation could predict primary failure of AVF, most studies have predicted secondary failures.

The study done by Zadeh et al. showed that CRP was positive in 34 patients (61.8%) with unsuccessful fistula function, while only 4 (7.3%) of those with successful AVF had positive CRP and the rest had negative CRP. The cut off values were kept as 200 nm/L. The difference between the two groups of patients was strongly significant ($p<0.001$) [17].

While several studies have shown the presence of diabetes, hypertension, female sex and increasing age as independent risk factors for primary failure of AVF, our study failed to do so [19-24].

Conclusion

In conclusion, our study has demonstrated that higher CRP levels can predict primary failure rates of an AVF with good sensitivity and specificity. Our study, however, has its limitations, firstly, in terms of being a pilot study with a small sample size of 44 patients, secondly, for excluding patients who underwent brachiocephalic and brachiobasilic fistulas and grafts. Hence, more studies are needed to confirm and validate the relationship between raised CRP levels and primary failure of AVF.

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