Risk Factors of Vascular Access Failure in Patients on Hemodialysis

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Introduction. The aim of this study was primarily to determine if there was any relationship between hemoglobin levels and vascular access (VA) survival. In addition, other risk factors were evaluated with special stress on sex, age, diabetes mellitus, smoking, and medications.

Materials and Methods. This study comprised 200 patients who had been on renal replacement therapy for more than 1 month through a permanent VA. The patients were categorized based on their mean blood hemoglobin levels. The possible risk factors for VA failure were also evaluated which included age at the beginning of hemodialysis, sex, diabetes mellitus, baseline levels of intact parathyroid hormone, and antihypertensive therapy with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Results. The younger the age the longer the duration of survival of left radial, left brachial, and right radial fistulas; however, sex had no significant impact on the duration of fistulas. Diabetic patients were more likely to have failed VA compared to nondiabetics. In addition, optimization of hemoglobin levels between 10 g/dL and 12 g/dL was associated with longer fistula survival. A higher risk of right radial arteriovenous fistula failure among hypertensive patients who received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers compared to those without these drugs.

Conclusions. Severe anemia, age, diabetes mellitus, and smoking are the main risk factors of VA failure. Our study showed that patients on hemodialysis should benefit from anemia correction, with a target hemoglobin level between 10 g/dL and 12 g/dL, without incurring any increased risk of VA failure.

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INTRODUCTION

Anemia is a characteristic and an important clinical manifestation of progressive kidney diseases. It usually worsens with the development of kidney failure, and it can be corrected with recombinant human erythropoietin. Although erythropoietin has been used in patients on dialysis since 1989, a global consensus regarding the optimum hematocrit target in this patient population has not yet been established. Indeed, the appropriate target hematocrit for patients on hemodialysis has been one of the most debated issues in nephrology throughout the past decade. Guidelines have suggested a hematocrit of 33% to 36% and a target hemoglobin (Hb) greater than 11 g/dL, with an average value of 12 g/dL to 12.5 g/dL.[1,2] However, many studies

have shown that by maintaining the Hb of these patients at nearly normal levels, great advantages in terms of quality of life, cardiac function, brain function, hospitalization, and costs can be achieved without significant adverse effects.[3-6] Nevertheless, there have been some concerns that full correction of anemia in patients on dialysis may increase the risk of adverse effects such as vascular access (VA) thrombosis.[7]

Hayakawa and colleagues[8] reported that the age, sex, and diabetes mellitus were risk factors for successful maintenance of the initial permanent hemodialysis VA. However, these factors were not related to the successful maintenance of a revised VA. Retrospective studies suggest that the use of angiotensin-converting enzyme inhibitors (ACEIs) in patients with polytetrafluoroethylene grafts might prolong and maintain VA patency. Fistula patency was affected by gender, with longer patency noted in males.[9] Moreover, Grandaliano and coworkers[10] suggested that hyperparathyroidism, smoking habits, cytomegalovirus infection and erythropoietin, independently of the hematocrit achieved, were independent risk factors of thrombosis in arteriovenous fistulas.

The aim of this study was primarily to determine if there was any relationship between Hb levels and VA survival. In addition, other risk factors were evaluated with special stress on sex, age, diabetes mellitus, smoking, and treatment with ACEI or angiotensin receptor blocker (ARB).

MATERIALS AND METHODS

We evaluated all patients with end-stage renal disease (ESRD) who started hemodialysis in our hemodialysis units (4 units) of Mansoura Urology and Nephrology Center, in Mansoura, Egypt. This study comprised 200 patients with ESRD who had been on renal replacement therapy for more than 1 month through a permanent VA during the period between 2000 and 2005 in our dialysis units. The database regarding demographic and clinical information of the patients admitted to our hemodialysis units were prospectively collected and continuously updated. It contained detailed information on VA with respect to the date of surgery, type of access, access site, date of failure, and all access-related complications. Patients with either autologous arteriovenous fistulae (AVF) or artificial grafts were considered. We excluded those with antiphospholipid syndrome, long-term central venous catheters, and failed fistulas due to technical defects. The patients were categorized into 3 groups based on their mean Hb levels during follow-up: group 1, Hb ranged from 6 g/dL to less than 10 g/dL; group 2, Hb ranged from 10 g/dL to <12 g/dL; and group 3 Hb level greater than 12 g/dL.

The majority of AVFs were created by one surgeon and routinely all cases with failed vascular access were maintained on antiplatelet therapy (aspirin 150 mg/d). Vascular access survival was defined as the length of the intervention-free period to the first failure. To test the predictive role of Hb level, survival analyses were conducted using the date of the first venipuncture for the initiation of hemodialysis. We selected the possible risk factors of VA failure which included age at the beginning of hemodialysis, sex, diabetes mellitus (type 1 or 2), baseline levels of intact parathyroid hormone (iPTH), and antihypertensive therapy by ACEI or ARB.

Statistical Analyses

The chi-square test was used for comparisons of categorical data between the groups. Risk factors related to patients' demographics and comorbid conditions were also considered. The survival functions of the AVF were studied using the Kaplan-Meier method and the between-groups differences by means of the log-rank test or the multiple comparison test. The AVF creation date was considered as the starting point, while the first AVF failure as the event. The Cox proportional hazard regression was used to model time to event as a function of age, laboratory variables, and the categorical covariates significantly related with the events. The estimated relative risk (RR) and its 95% confidence interval (CI) were calculated using the estimated regression coefficients and their standard errors. The covariates contribution to explaining the event was assessed by a 2-tailed Wald test. All the statistical analyses were performed using the SPSS software (Statistical Package for the Social Sciences, version 11.5, SPSS Inc, Chicago, Ill, USA). All values were expressed as mean ± standard deviation for continuous parametric data. Values of P less than .05 were considered significant.

RESULTS

The mean age of the patients was 40.0 ± 12.1

years, and the majority of them (56%) were younger than 40 years. Table 1 shows the characteristics of the patients. Most of them were suffering from secondary hyperparathyroidism. Hypertensive patients represented 76% of the study population, with nearly one-quarter of them receiving an ACEI or ARB in addition to 2 other antihypertensive agents.

Younger patients had longer survival of the left radial, left brachial, and right radial AVFs ($P < .001$). However, no significant difference in age groups could be detected with the right brachial fistula survival ($P = .17$; Table 2). Tables 3 and 4 show that sex had no significant impact on the mean duration of fistula survival, wherever its site of creation. The right radial AVF survived longer among patients aged between 40 and 60 years than that among younger patients (109 months versus 74 months, $P = .03$). On the other hand, the left brachial AVF survived longer (28 months) in patients younger than 40 years ($P = .001$). Both left and right radial AVFs had a longer survival in nondiabetics than diabetics and in patients with an Hb greater than 10 g/dL than those with lower Hb levels ($P = .001$). However, the left brachial AVF survived longer in nondiabetics ($P = .03$). Similarly, right radial AVFs of hypertensive patients who received an ACEI or ARB survived slightly longer compared to those without these drugs (Figure 1, $P = .05$). The left brachial and right radial AVFs survived longer in nonsmokers than smokers ($P = .001$; Figure 2).

In multivariate analysis, the RR of AVF failure in severely anemic patients was 1.80 (95% CI, 1.10 to 2.86) times higher than in the patients with an Hb level between 10 g/dL and 12 g/dL ($P = .01$).

Table 1. Characteristics of Studied Patients on Hemodialysis Through an Arteriovenous Fistula*

Characteristic	Value
Number of patients	200
Sex	
Male	168 (84)
Female	32 (16)
Mean age, y	40.0 ± 12.1 (21 to 60)
Age > 40 years	112 (56)
Smoker	56 (28)
Diabetic	48 (24)
Antihypertensive user	
No	48 (24)
1 drug	80 (40)
2 drugs	48 (24)
> 2 drugs	24 (12)
ACEI or ARB user	24 (12)
EPO user	140 (70)
Laboratory tests	
Hemoglobin, g/dL	10.6 ± 2.0 (9.2 to 13.2)
Hematocrit, %	33.0 ± 6.3 (27.1 to 39.1)
Platelet count, × 10^3/L	204.0 ± 84.0 (150 to 260)
Serum LDL-C, mg/dL	102.2 ± 12.2 (70 to 145)
Serum triglyceride, mg/dL	94.0 ± 58.0 (87 to 189)
Serum ferritin, ng/mL	79.6 ± 47.0 (47 to 130)
Serum iPTH, ng/mL	718.0 ± 120.0 (78 to > 2500)

*Values in parentheses are percentages for categorical data and range for continuous variables. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EPO, erythropoietin; LDL-C, low-density lipoprotein cholesterol; and iPTH, intact parathyroid hormone.

Table 2. Fistula Survival in Different Age Groups

Age Group, y	Number of Patent Fistulas During Follow-up Intervals, mo					*P*
	< 12	12 to 24	24 to 40	48 to 96	> 96	
Left Radial Fistula (n = 200)						
15 to 39	32	8	8	24	24	
40 to 59	8	0	40	16	8	
≥ 60	0	8	8	8	8	< .001
Right Radial Fistula (n = 48)						
15 to 39	0	0	8	0	0	
40 to 59	8	8	16	0	0	
≥ 60	8	0	0	0	0	< .001
Left Brachial Fistula (n = 144)						
15 to 39	24	16	17	23	15	
40 to 59	0	3	14	31	8	
≥ 60	0	7	1	8	0	< .001
Right Brachial Fistula (n = 41)						
15 to 39	23	0	0	0	0	
40 to 59	16	2	0	0	0	
≥ 60	0	0	0	0	0	.17

Table 3. Factors Influencing Radial Fistula Survival*

Factor	Left Fistula		Right Fistula	
	Mean Survival, mo	*P*	Mean Survival, mo	*P*
Sex				
Male	94		98	
Female	80	.23	84	.24
Age, y				
15 to 39	81		74	
40 to 59	88		109	
≥ 60	32	.35	8	.03
Diabetes mellitus				
Positive	83		91	
Negative	119	< .001	111	< .001
Smoking				
Positive	98		85	
Negative	90	.33	122	.001
Hemoglobin, g/dL				
< 10	78		73	
≥ 10	98	.01	108	.001
ACEI or ARB use				
Positive	67		75	
Negative	74	.51	57	.05

Table 4. Factors Influencing Brachial Fistula Survival*

Factor	Left Fistula		Right Fistula	
	Mean Survival, mo	*P*	Mean Survival, mo	*P*
Sex				
Male	24		23	
Female	0	…	26	.30
Age, y				
15 to 39	28		20	
40 to 59	18		22	
≥ 60	16	< .001	0	.61
Diabetes mellitus				
Positive	4.5		26	
Negative	28	.03	23	.47
Smoking				
Positive	17		47	
Negative	31	< .001	24	.08
Hemoglobin, g/dL				
< 10	23		28	
≥ 10	25	.50	22	.16
ACEI or ARB use				
Positive	16		19	
Negative	0	…	20	.90

*Ellipses indicate not applicable.

Table 5 shows that the largest number of patients with longer duration of fistula survival was among those with an Hb ranged from 10 g/dL to 12 g/dL (P = .001). Other major factors influencing VA survival included age (RR, 1.93; 95% CI, 0.94 to 2.9; P = .007), diabetes mellitus (RR, 3.1; 95% CI, 0.98 to 5.02; P = .02), smoking (RR, 2.5; 95% CI, 0.88 to 4.12; P = .02), and iPTH (RR, 1.5; 95% CI, 1.10 to 2.21; P = .01). Treatment with ACEIs or ARBs, however, was not a significantly influential factor (RR, 0.45; 95% CI, 0.20 to 0.98; P = .06).

Significant inverse correlations were found between the patients' age and the left brachial fistula survival (r = -0.696; P < .001), between

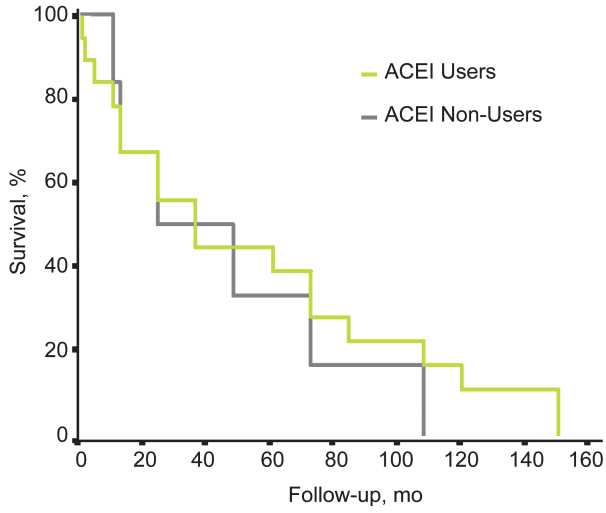

Figure 1. Effect of angiotensin-converting enzyme inhibitor (ACEI) on fistula survival (P = .05).

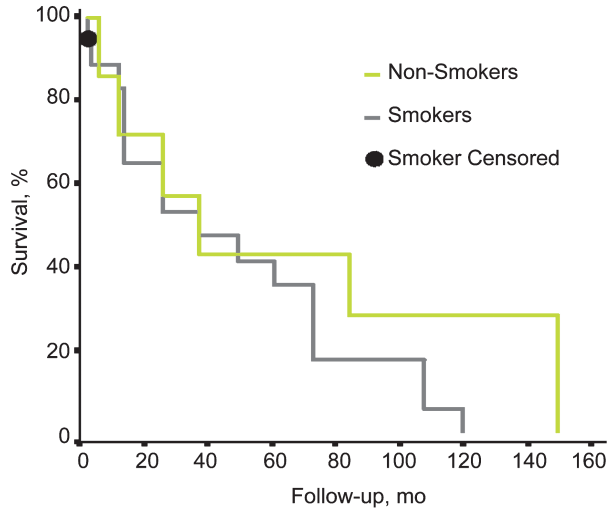

Figure 2. Effect of smoking on fistula survival (P < .001).

Table 5. Relation of Arteriovenous Fistula Survival and Hemoglobin Levels (P = .001)

	Number of Patent Fistulas During Follow-up Intervals, mo				
Recoded Hemoglobin, g/dL	< 6	6 to < 12	12 to < 24	24 to < 36	> 36
6 to < 10	8	8	8	10	30
10 to < 12	8	16	8	0	72
12 to 15	0	0	0	8	24
Total	16	24	16	18	126

platelet number and duration of survival of both distal and left brachial fistulas (r = -0.540, P < .001; r = -0.480, P < .001; respectively). In addition, a significant inverse correlation was detected between the number of antihypertensive drugs and the right radial AVF survival (r = -0.288, P < .001).

DISCUSSION

Vascular access morbidity is still elevated in patients on long-term hemodialysis whose health-related costs are increasing.[11-16] These contrasts with the efforts that nephrologists are making to reduce hemodialysis-related expenditure. In addition to the negative economic impact, the malfunctioning of the VA deteriorates the clinical outcome of patients who are exposed to inadequate dialysis performances and to infectious risks due to the temporary placement of catheters.[17] In this prospective study, we analyzed the impact of comorbidities on the primary survival of the AVF, which constitutes the most frequently used VA for hemodialysis in Egypt. We found that sex had no impact on fistula survival, wherever the site of creation, a finding that was not matched with some recent reports indicating that women had poorer distal AVF survival.[18-20] This could be explained by the high incidence of manual works in our female patients.

Regarding the classic atherogenic risk factors (diabetes mellitus and age), we found that the younger the patient, the longer the duration of survival of the left radial, left brachial, and right radial fistulas (P < .001). Also diabetics mellitus was associated with a higher frequency of fistula failure. These findings were in agreement with that reported by Garrancho and colleagues.[17] Hayakawa and coqworkers[8] reported that age was a risk factor for the successful maintenance of initial permanent hemodialysis VA. Other risk factors in their study included sex and diabetes mellitus, the former of which, however, failed to be risk factor in our study.

The potential association between VA thrombosis, higher Hb levels, and erythropoietin therapy, however, remains controversial. In our study, we found significant differences in autologous fistula survival in patients with Hb levels below 10 g/dL and above 10 g/dL, especially with the distal

fistulas. We assume that optimization of Hb levels between 10 g/dL and 12 g/dL is associated with longer fistula survival. Vascular access survived longer in less anemic patients than among severely anemic patients. However, we found no significant differences in VA survival among those with proximal fistulas. This result was in conflict with a previous large-sample randomized clinical trial published by Besarab and colleagues.[21] They concluded in their "Normal Hematocrit Cardiac Trial" that normalization of the Hb levels in patients on hemodialysis was not justified. Such results conflicting with ours might be explained by the fact that most of the patients in the Besarab and associates' study had grafts, whereas in our study, most patients had autologous AVFs. Another relevant difference is the design of the study. The former is an interventional trial with patients randomly forced to reach a certain Hb level. Our study, however, is an epidemiological evaluation in which the target Hb was established according to the *European Best Practice Guidelines*,[1] but the physicians were not forced to normalize Hb in patients resistant to correction.

On the other hand, our finding that severe anemia was associated with a higher risk of VA failure can be explained by the association of the anemic state with inflammatory states and the presence of comorbidities in many patients on hemodialysis. This hypothesis was in keeping with the findings of a study by Miller and colleagues[22] who found a shorter graft survival in patients with hypoalbuminemia compared with patients with normal serum albumin levels. Patients with inflammatory states would have erythropoietin resistance, and thus, lower Hb levels. Moreover, this inflammatory state would increase the likelihood of access failure. These two opposing effects would be obscured in a randomized study, given that no correlation between patients' Hb levels and the likelihood of access thrombosis was observed. Accordingly, in another randomized controlled trial, Foley and coworkers[23] found no difference in the incidence of VA thrombosis in patients with low Hb (9.5 g/dL to 10.5 g/dL) compared to those with normal Hb levels (13.0 g/dL to 14.0 g/dL).

We observed better survival of autologous AVF, although it did not rank to significance, among hypertensive patients who were maintained on ACEI or ARBS compared to those who were not maintained on these drugs. Our results were achieved in autologous VAs. The effect of these drugs was more prominent in a report by Garrancho and coworkers[17] who indicated that treatment with ACEIs or ARBs was associated with longer VA survival. The protective effect of ACEI has already been described in the literature; Saran and collegues[24] found a significant reduction of the risk of fistula failure with the use of ACEIs. Moreover, Sajgure and associates[9] suggested that using ACEI in patients with polytetrafluoroethylene grafts might prolong and maintain patency. High iPTH represented another important risk factor for VA thrombosis among our cohort, and this was matched with that reported by Morena and colleagues.[25]

CONCLUSIONS

Severe anemia (Hb level lower than 10 g/dL), age (older than 60 years), diabetes mellitus, and smoking were risk factors for access failure in our study. However, sex and treatment with ACEIs or ARBs had no significant impact on fistula survival. Our study showed that patients on hemodialysis should benefit from anemia correction, with a target Hb level between 10 g/dL and 12 g/dL, without incurring any increased risk of VA failure.

CONFLICT OF INTEREST

None declared.

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