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Factors Associated with Secondary Functional Patency After Percutaneous Transluminal Angioplasty of the Early Failing or Immature Hemodialysis Arteriovenous Fistula

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Abstract
Purpose To evaluate the efficacy of percutaneous transluminal angioplasty for early failing hemodialysis arteriovenous fistulas (AVFs) and predictors of secondary functional patency (FP).
Methods A review of our endovascular registry database showed that 61 patients with early failure after a surgically created AVF underwent endovascular intervention between 2011 and 2016. Median time from AVF creation to first intervention was 5.6 weeks. Median duration of follow-up was 14 months. Items related to the technical success rate and primary and secondary FP, and factors associated with secondary FP were analyzed.
Results Technical success was achieved in 55 (90%) of 61 patients. The primary and secondary FP rates were 42% and 65% at 12 months, respectively. Multivariate analysis showed that lesion length (HR; 1.15, $P = 0.001$) and lesions including juxta-AVF (the portion of fistula vein within 2 cm of the arteriovenous anastomosis, HR; 6.23, $P = 0.008$) were factors associated with reduced secondary FP. ROC curve analysis indicated lesion length with cutoff value ≥ 9 cm as a risk factor for reduced secondary FP. Secondary FP at 12 months for patients with no risk factors, with 1, and with 2 was 86%, 65%, and 0%, respectively. There was a significant difference in secondary FP rates among these groups ($P = 0.001$).
Conclusions A lesion length and juxta-AVF lesion are the risk factors for reduced secondary FP. The secondary FP rate at 12 months is acceptable in patients without risk factors.

Keywords Percutaneous transluminal angioplasty · Hemodialysis arteriovenous fistula · Early failing hemodialysis shunt · Functional patency · Predictive factor

Introduction

The kidney disease outcomes quality initiative (KDOQI) guidelines report an arteriovenous fistula (AVF) as the reference standard for primary vascular access because of longer life spans and a low incidence of infection compared with an arteriovenous graft (AVG) [1]. However, several studies showed that surgically created AVFs have high rates of early failure [2, 3]. Such patients frequently require surgical or endovascular interventions. The effectiveness of percutaneous transluminal angioplasty (PTA) is controversial for early failure of surgically created AVFs because of the shorter functional time gained and the higher rates of re-interventions, although it is useful for the dysfunctional matured AVF [4–7]. Furthermore, the risk factors for secondary functional patency after PTA for early failure of AVFs have not been well documented, whereas several

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studies have reported the risk factors for patency after PTA for late failure of AVFs [4, 6–8].

The purpose of this study was to evaluate the efficacy of PTA for early failing hemodialysis AVFs and to identify the predictors of secondary functional patency.

Materials and Methods

Study Population

This study was performed retrospectively by examining our endovascular registry database. Early failure was defined as an AVF that never developed to the point that it could be used or failed within the first 3 months of usage. According to a review of the endovascular registry database of our department, 450 consecutive patients with functional failure of a hemodialysis shunt underwent PTA between July 2011 and October 2016. During this period, 61 of the 450 patients were treated as immature (n = 50) or early failure (n = 11) after a surgically created AVF.

All patients signed a consent form for treatment, and all study protocols were approved by our institutional review board.

Endovascular Procedure

All patients underwent a physical examination that included palpation and auscultation of the AVF. Every vascular access was also examined by color Doppler ultrasound before angiography to identify the significant lesion site and estimate the diameters of the artery and vein to select the appropriate balloon size. Angiography of the fistula was routinely performed through a retrograde brachial artery puncture with a 20-gauge needle. When the AVF or outflow vein was easily collapsible, or an arterial inflow lesion was definitively detected by color Doppler ultrasound, initial cannulation using a 20-gauge plastic cannula was done through an antegrade brachial artery puncture. Inflow artery, anastomoses, and veins were visualized in all cases. Diagnostic angiography helps to determine the access site for endovascular intervention. For endovascular treatments, a 4F sheath was inserted from a vein or brachial artery depending on the lesion site detected by diagnostic angiography. After injection of heparin (50 units/kg), the lesions were crossed with a 0.018-inch guidewire (Carry, UTM Co LTD, Toyohashi, Japan; Transcend, Boston Scientific Japan, Tokyo, Japan) or a 0.014-inch guidewire (Transcend, Boston Scientific Japan, Tokyo, Japan; or Cruise, Asahi Intech, Nagoya, Japan). We usually use the microcatheter (ARIELA, UTM Co LTD, Toyohashi, Japan) for the complex lesions. For occlusions, a guidewire was passed through the lesions under ultrasound guidance. Then, a balloon angioplasty catheter (Sphere Cross curve, Tokai Medical Products, Kasugai, Aichi, Japan; Sphere Cross straight, Tokai Medical Products, Kasugai, Aichi, Japan; Sterling, Boston Scientific Japan, Tokyo, Japan) was advanced over the wire, placed across the stenosis, and then inflated to the pressure required to obtain the disappearance of any waist on the balloon. Balloon size (3–5 mm) was chosen by pre-procedural ultrasound estimation of the diameter of a normal vessel segment adjacent to the lesion. Inflations were maintained for 180 s. If the arterial approach was chosen, the procedure was performed via the artery in most of patients. For patients with thrombosed occlusion, catheter-directed thrombolysis (CDT) using urokinase was performed after the guidewire was passed. A 3.6F PIT multi-sidehole infusion catheter (SENTAN Pharma Inc, Fukuoka, Japan) was used for CDT. The dose of urokinase used was 180,000 units. Then, angioplasty was performed for the residual stenosis. A postprocedure angiogram was then performed, and balloon dilatation was repeated for any residual stenosis. During this study period, transcatheter embolization of collateral veins was not performed.

Variables and Definitions

The anatomical variables were location, length, and lesion type. In terms of lesion location, the AVF was divided into four segments: the supplying artery, the juxta-anastomosis defined as the portion of fistula vein within 2 cm of the arteriovenous anastomosis (juxta-AVF), cannulation zone, and outflow vein (OFV). Based on angiography and ultrasound findings, the vascular lesions were categorized as stenosis and occlusion with or without thrombosis. We measured the lesion length with reference of evaluations using ultrasound imaging with tourniquet, and indentation during balloon dilatation.

The PTA was considered technically successful if the degree of residual stenosis was less than 30%. Primary functional patency for immature AVF was defined as the ability to perform full dialysis treatment without any intervention after PTA. Primary functional patency for early failing AVF was defined as uninterrupted patency after intervention until the next access thrombosis or repeat intervention. Secondary functional patency was defined as patency until permanent access failure regardless of the number of endovascular interventions. The nephrologists followed up all patients after angioplasty, and the nephrologists determine whether the access for dialysis can be used. Follow-up protocol after PTA does not exist in our hospital. It depends on the nephrologist's assessment. We reviewed all charts in this study.

Statistical Analyses

Lesion type, lesion location, and technical success rates are presented as simple percentages. Primary and secondary functional patency rates were estimated by Kaplan–Meier analysis. Predictors of primary and secondary functional patency were evaluated by uni- and multivariate analyses using Cox proportional hazards regression. Candidate predictors with $P < 0.10$ on univariate analysis were included in the multivariate model. Individual differences were considered significant for values of $P < 0.05$. Patient's age, sex, presence of diabetes, fistula age, lesion type (stenosis or occlusion), lesion length, and lesion including supplying artery, juxta-AVF, cannulation zone, or OFV, were evaluated as predictors of AVF patency. All statistical tests were performed using SPSS for Windows version 11.0 J software (SPSS, Chicago, IL, USA).

Results

Overall, 48% of the patients were male, with a median age of 68 years (range, 24–86 years). Diabetes mellitus was present in 51%. The fistulas were created at the radiocephalic region in 52 patients, the radiobasilic region in 2 patients, the ulnarbasilic region in 1 patient, and the brachiocephalic region in 6 patients.

The median time from AVF creation to first intervention was 5.6 weeks (range, 1–12 weeks). The median duration of follow-up was 14 months (0.4–71 months). We performed the ultrasound study for patients with immature AVF. If the ultrasound study demonstrates the significant stenosis or occlusions could affect the flow, angiography is performed even if AVF age is < 6 weeks.

Anatomical problems were identified in all 61 early failing AVFs, with the main lesions at the juxta-AVF and cannulation zone. Angiography showed 38 stenoses (62%) and 23 occlusions (38%). Median lesion length was 4.5 cm (range, 1–25 cm).

PTA was performed by a transvenous approach in most patients (49 patients; 80%) with careful puncture under ultrasound guidance. CDT was performed in six patients using urokinase (median dose, 12×10^4 units) for significant thrombosed occlusions. The characteristics of the patients are shown in Table 1.

PTA was technically successful in 55 (90%) of 61 patients. Failure of guidewire recanalization was detected in three patients, and the residual stenosis was greater than 30% in three patients. Complications occurred in three (5%) patients, including one extravasation during intervention and two arterial spasms. In the case of extravasation, hemostasis was achieved during the procedure, and arterial spasm did not affect AVF patency. All complications were considered minor. There were no major complications.

Table 1 Characteristics of the study population

Number of patients	61
Age	68 (24–86) years
Gender, male	29 (48%)
Diabetes mellitus	31 (51%)
AVF age	5.6 (1–12) weeks
First AVF for patient	41 (67%)
Immature	50 (82%)
Stenosis	38 (62%)
Occlusion	23 (38%)
Lesion length	4.5 (1–25) cm
Lesion location	
Single location	
Artery	3
Juxta-AVF	9
Cannulation zone	22
OFV	1
Multiple location	
Artery/Juxta-AVF	2
Artery/Juxta-AVF/CZ	1
Juxta-AVF/CZ	17
CZ/OFV	4
Juxta-AVF/CZ/OFV	2

All continuous variables are expressed as median (range)

Juxta-AVF—juxta arteriovenous fistula defined as within 2 cm of arteriovenous anastomosis, *CZ*—cannulation zone, *OFV*—outflow vein

Including the initial patients with technical failures, the primary and secondary functional patency rates at 12 months were 42% and 65%, respectively (Fig. 1). Univariate analysis using a Cox proportional hazards regression model showed that lesion length should be considered a risk factor for reduced secondary functional patency ($P = 0.009$). A relative tendency was seen for lesions including juxta-AVF to be associated with secondary functional patency on univariate analysis ($P = 0.057$). No other significant differences were seen on univariate analysis (Table 2). Therefore, lesion length and lesions including juxta-AVF were evaluated by multivariate analysis to identify factors associated with secondary functional access patency. Multivariate analysis using a Cox proportional hazards regression model (Table 2) showed that lesion length (hazard ratio 1.15, $P = 0.001$, 95% confidence interval 1.06–1.24) and lesions including juxta-AVF (hazard ratio 6.23, $P = 0.008$, 95% confidence interval 1.62–24.5) were factors associated with secondary functional patency.

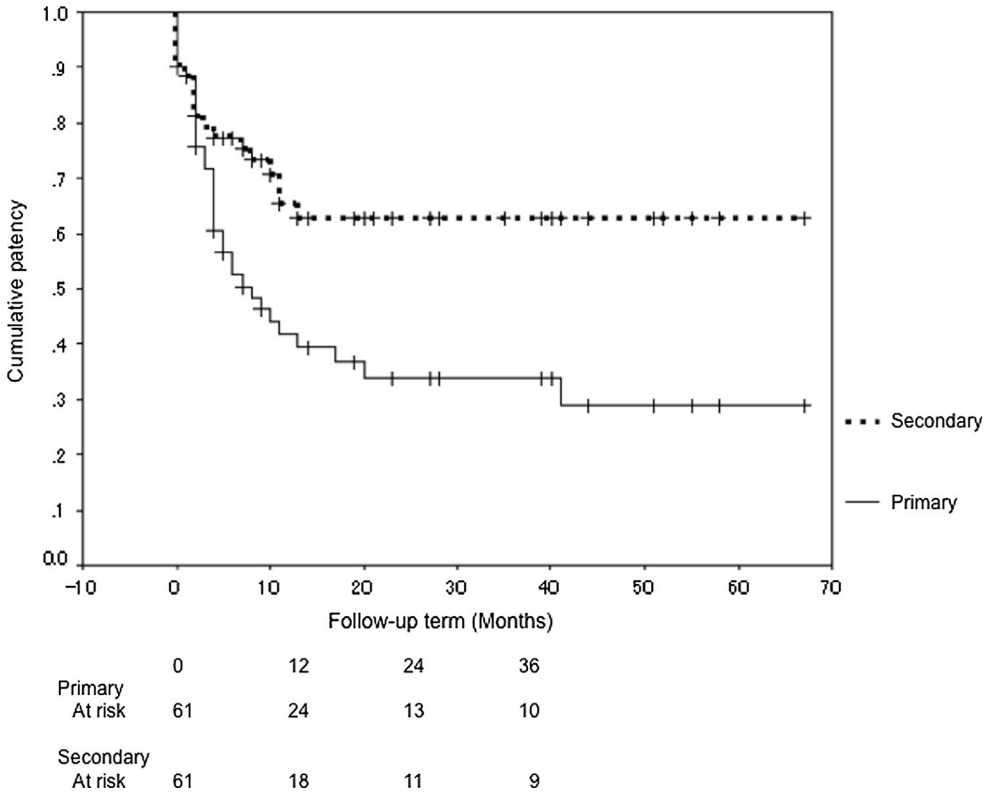

Fig. 1 Functional patency rates of early failing AVFs after PTA estimated by Kaplan–Meier analysis. A, Primary functional patency; B, secondary functional patency. The primary and secondary functional patency rates at 12 months were 42% and 65%, respectively

Table 2 Factors for secondary functional patency

Factors	Univariate		Multivariate	
	HR [95% CI]	*P*-value	HR [95% CI]	*P*-value
Age	1.00 [0.96–1.04]	0.992		
Sex (male)	0.59 [0.19–1.80]	0.351		
DM	0.60 [0.18–1.94]	0.389		
AVF age	1.10 [0.89–1.36]	0.396		
First AVF	0.75 [0.21–2.73]	0.665		
Immature	2.38 [0.31–18.34]	0.405		
Occlusion	1.22 [0.40–3.74]	0.730		
Lesion length(/cm)	1.10 [1.02–1.17]	0.009	1.15 [1.06–1.24]	0.001
Lesion including				
Artery	0.042 [0.00–100]	0.424		
Juxta-AVF	3.15 [0.97–10.27]	0.057	6.23 [1.62–24.47]	0.008
CZ	1.75 [0.39–7.93]	0.468		
OFV	1.44 [0.32–6.50]	0.636		

HR—hazard ratio, 95% *CI*—95% confidential interval, *DM*—diabetes mellitus, *AVF*—arteriovenous fistula, *CZ*—cannulation zone, *OFV*—outflow vein

ROC curve analysis indicated that lesion length with a cutoff value $\geq$ 9 cm was a risk factor for reduced secondary functional patency. Secondary functional patency at 12 months was 86% for patients with no risk factors (n = 23), 65% for patients with 1 risk factor (n = 33), and 0% for patients with 2 risk factors (n = 5) (Fig. 2). There was a significant difference in the secondary functional patency rate among these groups (P = 0.001).

Discussion

According to the present study, the initial procedure results were satisfactory, with a high technical success rate (90%) and a low complication rate (5%). The primary patency rate after PTA in the present study was 42% at 12 months, which is comparable to the primary patency for patients an early failed AVF (28–68%) reported by the previous

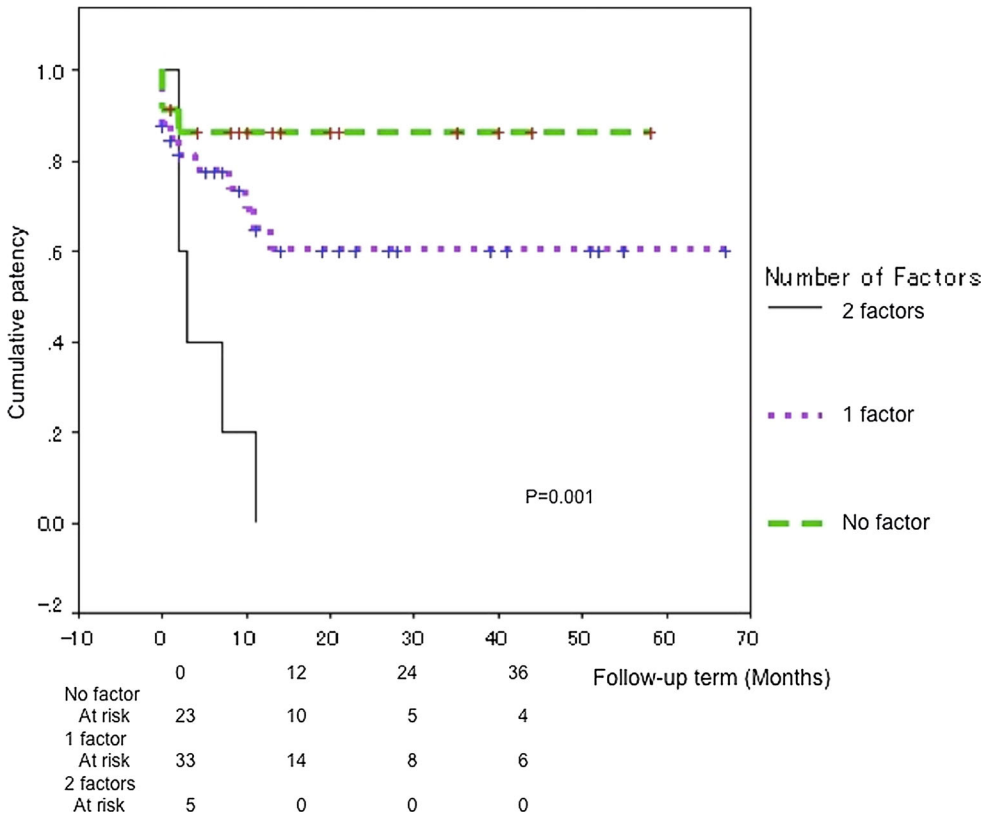

Fig. 2 Secondary functional patency rates of early failing AVFs after PTA by the number of risk factors. Secondary functional patency at 12 months was 86% for patients with no risk factors ($n = 23$), 65% for patients with 1 risk factor ($n = 33$), and 0% for patients with 2 risk factors ($n = 5$). There was a significant difference in the secondary functional patency rate among these groups ($P = 0.001$)

studies [4, 8–13]. On the other hand, the secondary patency rate in the present study was 65%. The previous studies of PTA in patients with a matured (late) failed AVF indicated that the secondary patency rates were 83–90% [6, 7, 10, 14–16]. Also, the secondary patency rate after PTA in patients with early AVF failure was 68–85% [4, 8, 10–13]. Thus, the present secondary patency rate is inferior to those reported in the past studies for matured (late) AVF failure, though comparable to the secondary patency for early AVF failure reported by the previous studies. Manninen et al. [4] evaluated the utility of endovascular salvage of nonmature AVFs in a prospective trial compared with that of mature AVF failure. They showed that the secondary patency rate of nonmaturing fistulas was worse than that of mature fistulas, although the primary patency rate for nonmaturing AVFs was not significantly worse than that for failing mature AVFs. The secondary functional patency in the present study (65%) was similar to the result (68%) reported by Manninen et al [4]. On the other hand, Liang et al. [8] reported that their secondary patency after PTA for immature AVFs was almost equivalent to that for mature AVFs reported by Manninen et al [4]. This discrepancy may result from the differences in the characteristics of the patient populations or lesions.

According to the present study, the factors associated with secondary patency are lesion length and lesion location (including juxta-AVF), although the risk factors for patency after PTA for early AVF failure were not well known previously. Tham et al. studied patency and predictive factors after endovascular salvage of nonmaturing AVFs [13]. Their report indicated that patients with preoperative vein size > 2.0 mm and age < 55 years were more likely to achieve clinical success, but these results were not significant [13]. Liang et al. [8] concluded that vascular rupture that occurred during the procedure was predictive of short primary patency. Manninen et al. showed that a small (< 3 mm in diameter) inflow artery was a predictor of poorer primary patency [4]. However, most interesting would be the factors associated with secondary patency, because several studies showed poorer secondary patency rates for early AVF failure [4, 12, 13], but not for initial success or primary patency compared with late AVF failure, similar to the present results. The present study showed that longer lesion length predicted poorer secondary patency. While several reports of late dysfunctional AVFs have already demonstrated that the extent of the lesion is an important predictor of patency after PTA [14–16], the present study showed a similar result in patients with early AVF failure. The AVFs in the present series failed early (within 3 months) or never matured to sustain HD after creation. Therefore, vascular injury or neointimal hyperplasia induced by HD must have been minimal at the time of PTA. Further, AVFs with

diffuse lesions may have a suspicious artery or vein at the time of creation. This result can support the importance of more careful preoperative surveys of the artery and vein by duplex ultrasound [1] to prevent secondary access failure after PTA, as well as early AVF failure after creation. The length of lesion as a continuous variable was a significant predictor for secondary functional patency. The ROC curve analysis showed that lesion length $\geq$ 9 cm was a cutoff value for reduced secondary functional patency. This cutoff value is relatively long compared to that reported previously.

The other risk factor for secondary patency shown by the present study was a lesion including juxta-AVF. Several studies demonstrated that the location of lesions results in differences in patency after PTA. The study to evaluate the utility of PTA for nonmaturing AVFs due to inflow arteries by Raynaud et al. [17] demonstrated that primary patency was much better for forearm arteries. Moreover, a juxta-AVF lesion has been reported as a problematic location for patency after PTA of failing mature AVFs [18]. The previous meta-analysis of late dysfunctional AVFs suggested that surgery is the best way to treat juxta-anastomotic stenosis [19]. As a result, surgical repair may be the preferred option for the juxta-anastomotic stenosis of early failure.

Secondary functional patency at 12 months was 86% for patients with no risk factors (without a longer lesion of $\geq$ 9 cm in length or a juxta-AVF lesion) and 0% for patients with 2 risk factors. The secondary patency rate for AVFs without risk factors was well and comparable to that for matured AVFs, although that in the patients with two factors was quite low. These findings could contribute to the decision making for patients with immature AVF.

The etiology of immature AVFs is still debated. The most common identifiable causes for early failure after AVF creation may be vascular stenosis including the anastomosis and the presence of accessory or branch veins. Vascular stenosis or occlusion must be treated. The role of obliteration of accessory veins is controversial, although several investigators showed that accessory veins are a cause of immature AVFs [9]. In the present study, the population never embolized a collateral accessory vein. Patients in the present study underwent pre- and post-PTA angiography, and significant stenosis or occlusions that resulted in early failure were detected in all patients. Several investigators have already reported similar findings [4, 8, 20]. The presence of an accessory vein could also be beneficial to provide additional vessel cannulation in case the original puncture segment is lost.

The present study had a few limitations. The first limitation lies in the design of this study, which was a case series with a relatively small number of patients. Therefore, several relevant characteristics of the population were lacking, for example, preoperative arterial and venous diameters and postoperative drug administration including antiplatelet therapy. Second, the follow-up term was relatively short (median follow-up 14 months). Third, the prevalence of nonmaturing AVFs during the study period was unknown. These limitations might weaken the impact of this study. A prospective study would help to clarify the issues associated with PTA for early AVF failure after surgical creation.

In conclusion, lesion length and a juxta-AVF lesion are the risk factors for reduced secondary functional patency. The secondary functional patency rate at 12 months was acceptable in patients without risk factors.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent This study has obtained IRB approval from (indicate the relevant board), and the need for informed consent was waived.

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